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CYTOLOGIC EFFECTS OF THE LIGATION OF THE MAJOR BLOOD VESSELS OF THE KIDNEY OF THE ALBINO RAT *

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Following the pioneer work of Litten,[1] Talma,[2] Pollack,[3] Sacerdotti and Frattin,[4] Poscharissky,[5] and Liek,[6] Maximow[7] confirmed the observation that vasoligation of the kidney in the rabbit results in the formation of bone, especially in the region of the renal hilus. Maximow extended the investigation and described in addition myeloid metaplasia in the subepithelial region of the pelvis. He claimed that the red cell ancestors of the ectopic bone-marrow are pluripotential small lymphocytes that have become entrapped in the capillaries. Though Maximow consistently regarded the large lymphocyte as potentially identical with the hemoblast, this is the only place in which he ascribes erythrocytopoietic potency, via a large lymphocyte stage, to the small lymphocyte.

The primary object of our investigation was to test this conclusion by further experimental studies, in this case with the albino rat. We succeeded in effecting osseous metaplasia in the renal hilus in some

* Submitted for publication, June 28, 1930.

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1. Litten, M.: Untersuchungen über den haemorrhagischen Infarct und über die Einwirkung arterieller Anaemie auf das lebende Gewebe, Berlin, A. Hirschwald, 1879, ch. 1.

2. Talma, S.: Der Verschluss der Nierarterien und seine Folgen, Ztschr. f. klin. Med. **2**:483, 1881.

3. Pollack, K.: Beiträge zur Metaplasiefrage, Arb. a. d. path-anat. Abteilung d. k. hyg. Inst. zu Posen, Wiesbaden, J. F. Bergmann, 1901, pp. 154-204.

4. Sacerdotti, C., and Frattin, G.: Ueber die heteroplastische Knochenbildung; experimentelle Untersuchungen, Virchows Arch. f. path. Anat. **168**:431, 1902.

5. Poscharissky, J. F.: Ueber heteroplastische Knochenbildung; eine pathologisch-histologische und experimentelle Untersuchung, Beitr. z. path. Anat. u. z. allg. Path. **38**:135, 1905.

6. Liek, E.: Experimenteller Beitrag zur Frage der heteroplastischen Knochenbildung, Arch. f. klin. Chir. **80**:279, 1906.

7. Maximow, A. A.: Experimentelle Untersuchungen zur postfötalen Histogenese des myeloiden Gewebes, Beitr. z. path. Anat. u. z. allg. Path. **41**:122, 1907.

instances, but as regards the erythrocytopoietic capacity of the lymphocyte under these conditions our results are definitely negative. However, in the course of this work data accrued concerning especially the migration of fibroblasts and macrophages, regenerative changes in the kidney, and the origin of plasma cells and Russell body cells, all of which appear to us deserving of record.

MATERIAL AND METHODS

The material consisted of sixty-eight left kidneys of albino rats. These kidneys were of four types: normal kidneys with the major blood vessels ligated at the hilus; kidneys with an injection of trypan blue in the renal artery, followed in some cases by ligation of the major vessels, and kidneys from animals on which splenectomy and vasoligation had been done. The kidneys were removed after ligation for twenty-four hours, three days and from one to ten weeks. On autopsy, the kidneys were fixed in Helly's Zenker-formaldehyde solution. Kidneys of more than three weeks' ligation were decalcified in 3 per cent nitric acid alcohol. The material was embedded in paraffin and sectioned at 6 microns. Some sections were stained with hematoxylin-eosin-azure II according to the method of Maximow as given by McClung;[8] others, by the Foot silver technic for demonstration of reticulum. The unligated kidneys from the experimental animals, together with lymph nodes, spleen and bone-marrow, were fixed and stained in a similar manner. Wet smears were made from the cortices of kidneys at various stages of ligation. These were fixed and stained with hematoxylin-eosin-azure II according to the method of Bloom.[9] Smears from kidneys ligated for one, two and six weeks, respectively, were studied after supravital staining with neutral red and Janus green according to the method of Sabin.[10]

Pathologic kidneys of man were studied for comparative purposes. These showed infarction, chronic passive congestion, parenchymatous degeneration, arteriosclerosis, lymphosarcoma, colloid degeneration, amyloid formation and acute glomerulonephritis.

OBSERVATIONS

As stated in the introduction, this series of experiments demonstrates that myeloid metaplasia does not follow ligation of the major vasa of the kidney of the albino rat. Thus the major thesis which these experiments sought to demonstrate following Maximow's claim for the rabbit, viz., that under conditions of relatively slow circulation entrapped lymphocytes may metamorphose into red blood corpuscles, is not verified. No appreciable number of lymphocytes were entrapped in the vasa of the kidney following the ligation. Such lymphocytes as appeared in our material came in from a collateral circulation secondarily established and appearing usually three weeks

8. McClung, C.: Handbook of Microscopical Technique, New York, Paul B. Hoeber, 1929.

9. Bloom, W.: The Origin and Nature of the Monocyte, Folia haemat. **37**:1, 1923.

10. Sabin, F. R.: Studies of Living Human Blood Cells, Bull. Johns Hopkins Hosp. **34**:277, 1923.

after ligation. These lymphocytes migrated out of invading lymphatics of the capsule and superficial cortical region, and in the cortex changed into plasma cells and large lymphocytes. The plasma cells in turn became Russell body cells, but the large lymphocytes did not develop further. These cytologic changes began to occur during the third week of ligation and were progressively continuous throughout the experiments. The final picture of the ligated kidney in our series of experiments resulted from changes brought about by invading neutrophil granulocytes, fibroblasts, macrophages, blood vessels, lymphatics and lymphocytes. The striking feature in the majority of kidneys examined after the third day of ligation was the establishment of three independent zones: (1) a zone beneath the pelvic epithelium ("Rind-zone" of Maximow [7] in the rabbit); (2) a cortical zone enclosed in a thick capsule and separated from the next zone by a band of neutrophil granulocytes, and (3) a medullary zone. Changes in these three zones were independent of each other and varied with differences in the extent of the collateral circulation. In a brief description of the different zones, we can more readily indicate wherein our results differ from those of Maximow.

In the first zone, that beneath the pelvic epithelium, there is in the normal kidney a thin layer of collagenous fibers and fibroblasts directly connected with the perirenal tissue at the hilus. Internally, this layer extends to the base of the papilla, and its boundary is crossed by the renal tubules, which extend into the medulla from the more distal regions of the cortex. The larger vessels course in this tissue to reach the renal arcade. Following ligation, the arteries of this region were collapsed, and the veins were distended with red blood corpuscles. The surrounding fibroblasts enlarged and deposited coarse collagenous fibers. New vasa penetrated this layer from the hilus. A new circulation was set up, and the distended old veins became filled with an organizing thrombus. Few lymphocytes were seen to be entrapped here. There was no picture at any time resembling the conditions described by Maximow in which, in this particular region, the entrapped small lymphocytes changed into large lymphocytes and the latter into megaloblasts that finally gave rise to erythroblasts, normoblasts and erythroplastids. There was definitely a highly vascular area here of recent origin and established by ingrowing vessels. In several kidneys, one each of the fourth, fifth and ninth week, and two of the sixth week, of ligation, bone was present in this zone (fig. 1). Stages in the establishment of the bone by activity of the fibroblasts were observed. In this region of the rabbit's kidney, Maximow found metaplastic bone-marrow, but we found none. The changes here were independent of changes in the other parts of the kidney.

In the second or cortical zone, two types of changes were observed following ligation. In the normal kidney, this zone is enclosed in a

thin capsule of fibro-elastic connective tissue. The cortex contains the glomeruli, convoluted tubules and collecting tubules. The tubules are separated from each other by narrow blood spaces lined with reticulum (fig. 2 *A*). Only reticulum cells are found here, and these lie close against the homogeneous basement membrane of the tubules (fig. 5 *B*). In this interpretation of the interstitial stroma of the rat's kidney, we agree with Corner.[11] Fibroblasts are relatively scarce, and the blood

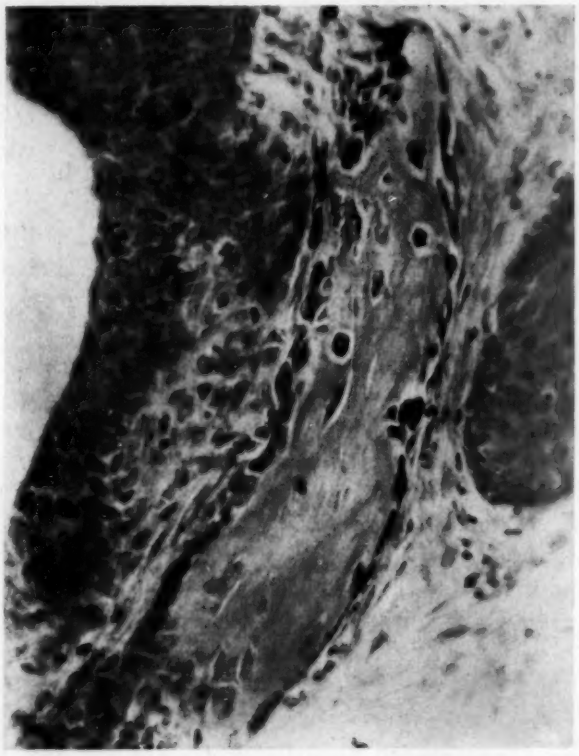

Fig. 1.—Vertical section through the pelvic mucosa of a kidney ligated for four weeks. Note the transitional epithelium of the pelvis on the left separated from the underlying metaplastic bone by a narrow layer of cellular connective tissue. Helly fixation; eosin-azure II; × 600.

spaces are usually occupied by red blood corpuscles. Striking changes took place in this region following ligation. After ligation for twenty-four hours, the blood spaces were distended with red blood corpuscles, and the tubules were pushed apart (fig. 3 *A*). In this distended condition, the ramification of the reticulum net and the homogeneous base-

11. Corner, G. W.: On the Widespread Occurrence of Reticular Fibrils Produced by Capillary Endothelium, Carnegie Inst., Contrib. Embryol. (no. 272) **9**: 85, 1920.

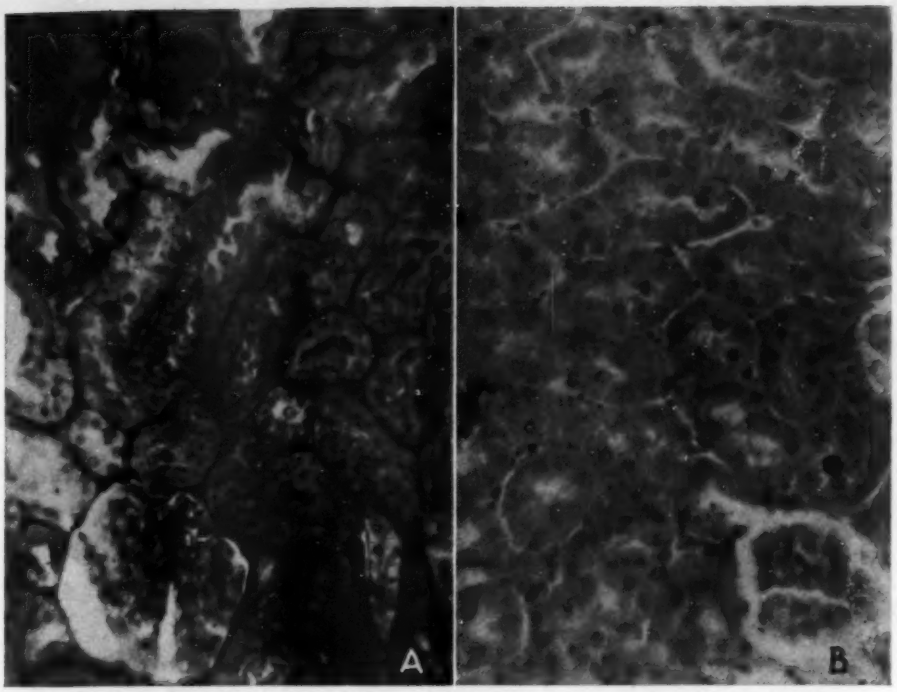

Fig. 2.—*A*, the cortex of the normal kidney of the albino rat. The reticulum between the tubules is black. *B*, the cortex of a normal kidney. Helly fixation; Foot reticulum technic for *A* and hematoxylin-eosin-azure II for *B*; × 350.

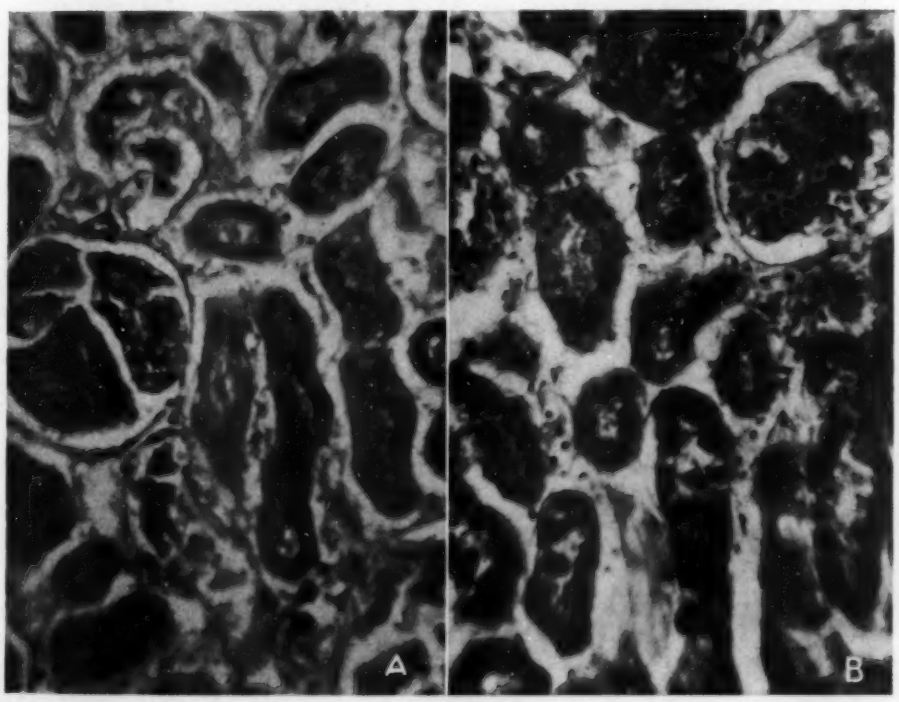

Fig. 3.—*A*, the cortex of a kidney ligated for twenty-four hours; *B*, for three days. Helly fixation; Foot technic; × 350.

ment membrane of the tubules and glomeruli could be distinctly observed. The renal epithelium was largely necrotic. After three days, the capsule began to thicken as the result of an increase in the number of fibroblasts and collagenous fibers, and there were accumulations of neutrophil granulocytes in the blood spaces nearest the cortex (fig. 3*B*). The neutrophil granulocytes seemed to be invading the cortex from the perirenal vasa. Fibroblasts, monocytes and macrophages were present between the tubules nearest the capsule (fig. 4).

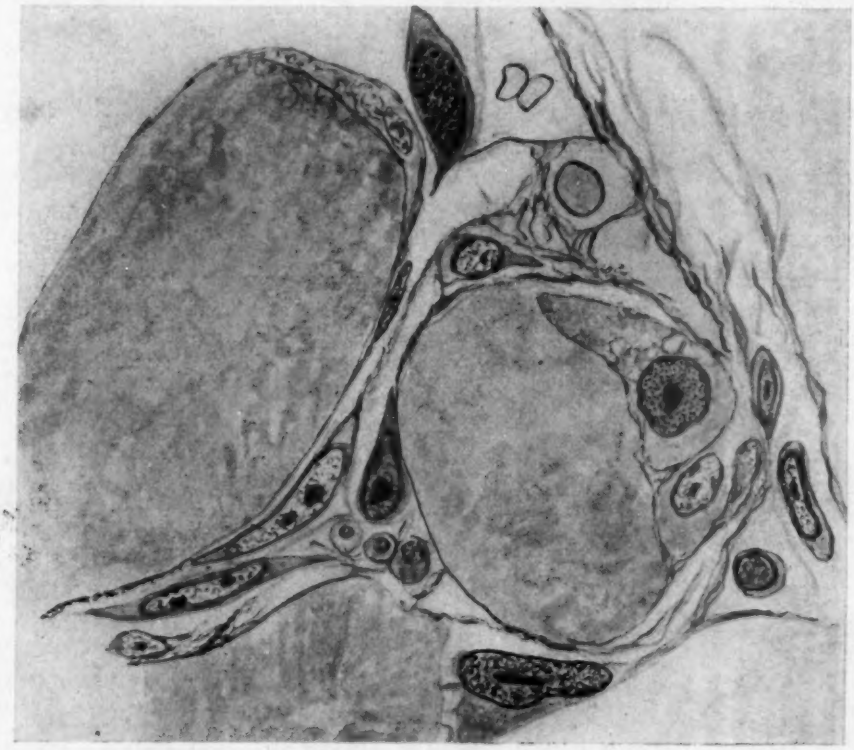

Fig. 4.—Drawing of a subcapsular region from the cortex of the kidney, after three days ligation. Note the fibroblasts and macrophages between the tubules, the macrophages within the tubules and the homogeneous remnants of the necrotic renal epithelium. Helly fixation; hematoxylin-eosin-azure II; × 1,350.

The fibroblasts were large, and many of them were in mitosis. Usually, they lay with the long axis at right angles to the capsule, thus giving the impression of migration into the cortex. Macrophages characterized by a foamy cytoplasm were present within some of the more peripheral tubules (fig. 5*A*). These macrophages were evidently destroying the remnants of the tubule epithelium. Many of the macrophages were in mitosis. The reticulum framework was as clear as in the normal kidney. No collagenous fibers were present.

In most of the kidneys ligated for one week, the capsule was very thick, and there was evidence of the beginning of a collateral circulation extending to the cortex from the perirenal vasa. In some kidneys, this was an extension of a branch of the inferior phrenic artery, and in others the collateral circulation arose from the splenic vessels. Fibroblasts, monocytes, macrophages, mast cells, neutrophil and eosinophil granulocytes, small lymphocytes and a few plasma cells lay between the collagenous fibers of the capsule. In the cortex, many of the tubules had disappeared, and their places were occupied by

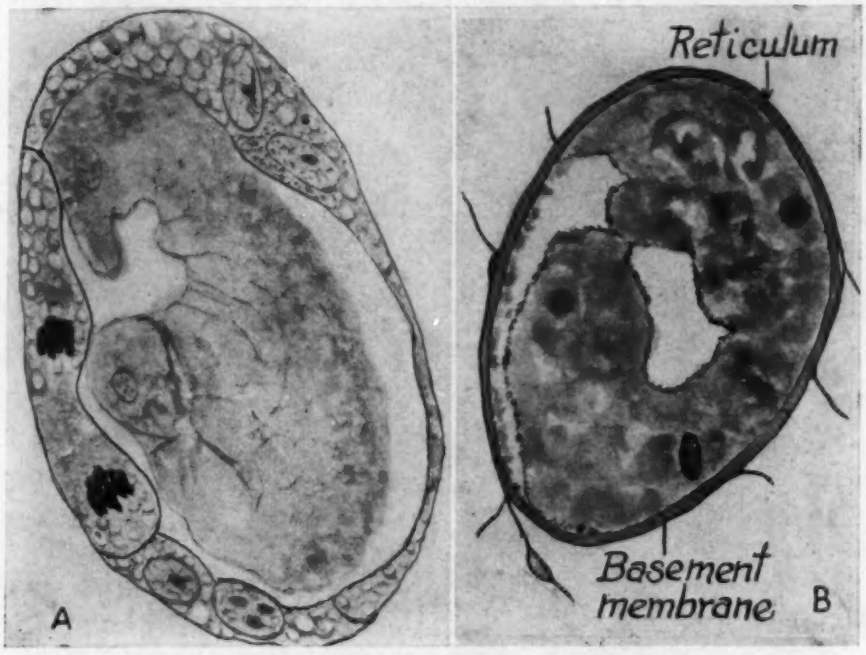

Fig. 5.—*A*, drawing of the cortex of a kidney after three days' ligation. Note the central necrotic renal epithelial remnants and the peripheral macrophages. One of the macrophages is in mitosis. *B*, drawing of a section of a tubule from the cortex of a kidney ligated for one week. Note the relation of the delicate reticulum fibers to the homogeneous basement membrane. Helly fixation; hematoxylin-eosin-azure II for *A* and Foot technic for *B*; × 1,350.

macrophages. In other regions, the tubules appeared as dull hyaline masses enclosed in a framework of reticulum (figs. 5 *B* and 6 *A*). The neutrophil granulocytes observed in the periphery of the cortex at the end of the third day of ligation had now penetrated deeper. In some kidneys, they formed a layer about half way between the capsule and the medulla; in others, they had reached the corticomedullary boundary.

The corticomedullary zone of neutrophil granulocytes was a distinct feature of practically all of the kidneys examined in the latest weeks of ligation. This zone separated an organizing neocortex from a necrotic, unorganizing medulla. The characteristic feature of the one week stage of ligation was the large size of the fibroblasts which filled the reticulum-lined spaces and which in a few places were surrounded by coarse collagenous fibers. From comparison of these in position and number with fibroblasts in the earlier stages of ligation, it was concluded that

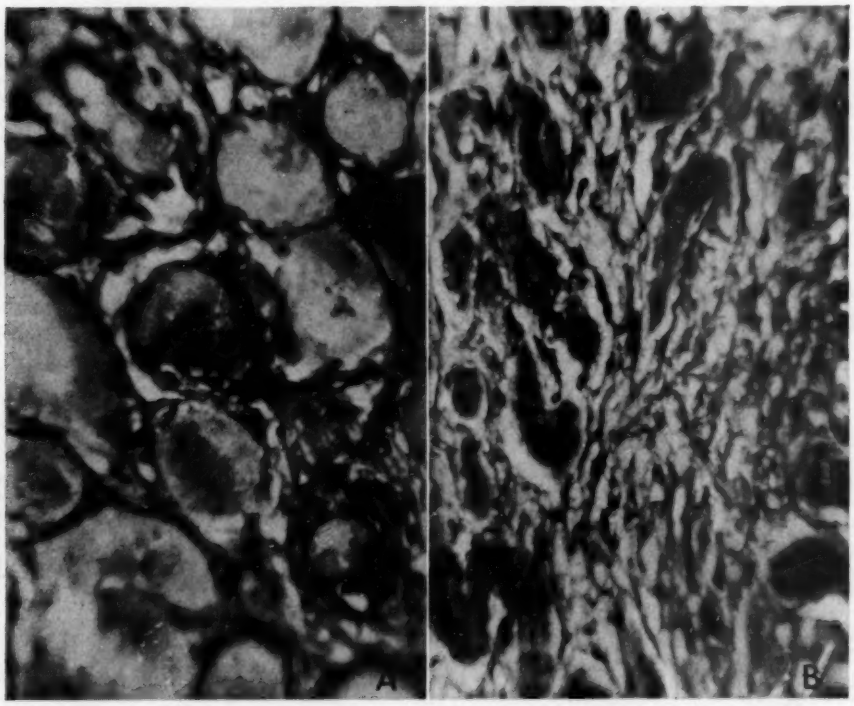

Fig. 6.—*A*, the cortex of a kidney ligated for one week; *B*, for two weeks. Helly fixation; Foot technic; × 600.

they were derived from fibroblasts which had invaded the interstitial tissue from the capsule, and that they did not arise from preexisting interstitial cellular elements. Furthermore, fibroblasts were distinct from macrophages, and no transition from one type to the other could be recognized.

The conditions following the second week of ligation were similar to those following the first, except for more collagenous fibers and more extensive replacement of tubules by macrophages (fig. 6*B*). Few tubules had the appearance of calcification, a feature characteristic of the tubules of the ligated kidney of the rabbit following one week of liga-

tion (Maximow[7]). The vasa present in the capsule of the kidney ligated for one week were represented in the kidney after two weeks' ligation by intracortical sprouts. The endothelial cells of these invading vasa were very large and were similar to the endothelial cells of the vasa that invade granulation tissue. There was no evidence that they became free and transformed into macrophages.

After two weeks' ligation and during the preceding stages, in kidneys into which trypan blue had been injected before ligation,

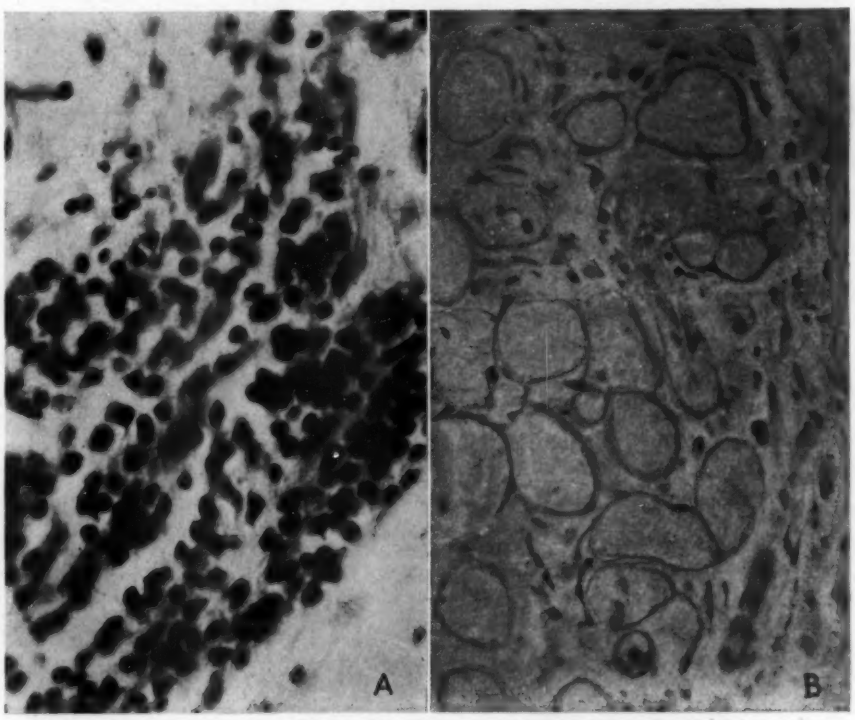

Fig. 7.—*A*, the cortex of a kidney ligated for three weeks × 600; *B*, for four weeks. Helly fixation; hematoxylin-eosin-azure II; × 350.

there was no indication that any of the interstitial elements were phagocytic. The trypan blue, when observed, was usually stored in the necrotic renal epithelial cells. The kidneys into which trypan blue had been injected and which had then been ligated and the simple ligated kidneys underwent the same type of modification. The invading fibroblasts, macrophages and vasa all stopped at the corticomedullary zone of neutrophil granulocytes. In this zone, the reticulum fibers had largely disappeared. Fibroblasts and macrophages apparently had no destructive effect on the reticulum fibers, but it seemed as though they might be digested by neutrophil granulocytes.

These same processes of increase in number of fibroblasts and macrophages, collagenous deposition and tubular replacement were present in the kidneys following the third week of ligation. In addition, lymphatics that to this time were not apparent in the cortex became visible by reason of distention with small lymphocytes (fig. 7*A*). They were just beginning to grow into the cortex from the capsule. The question arises as to whether they were lymphatics originally present which had become filled with lymphocytes because the normal egress through the hilus was lacking, or whether they were neoformations. From what is known of the course of the lymphatics through the kidney it would seem that the ligation of the vasa would have blocked the lymph flow and entrapped the lymphocytes. If this had been the case, however, we would expect the lymphatics to have been blocked immediately following ligation. Since there was no evidence of this, we interpret the lymphatic channels that appeared beginning with the third week of ligation as neoformations. In the region of the lymphatics were many free extravascular small lymphocytes, transition stages from small lymphocytes to large lymphocytes and to plasma cells. Transition stages between plasma cells and Russell body cells were also present. The Russell body cells were characterized by the cartwheel type of nucleus of the plasma cell and a cytoplasmic content of one or more eosinophil masses of various shapes (fig. 10*A*). From the sequence of changes described, the Russell body cells may be regarded as the end-cells of lymphocyte degeneration. They usually passed through the plasma cell stage first, but some cells resembling small lymphocytes contained the characteristic Russell bodies.

In most of the kidneys of the four week stage of ligation, the conditions of the three week stage were characteristic, with an increase of fibroblasts, collagenous fibers, lymphatics, lymphocytes, plasma cells, Russell body cells and macrophages. In one kidney, however, there was apparently little change in the cortex from that of the normal unligated kidney, except for necrosis of the tubules. These were colorless epithelial shells between which could be seen the reticulum cells and fibers (fig. 7*B*). None of the changes characteristic of the other kidneys had taken place. A few macrophages were present at one end of the cortex near the hilus. The explanation for this apparent static condition lay in the failure of development of a neocortical circulation. This in turn may have brought about the failure of invasion of the cortex by neutrophil granulocytes. From a study of our whole series, the neutrophil granulocytes seem to have been stimulators of further change as regards fibroblasts, macrophages and invading vasa. The static condition found here may have persisted because of the lack of an initial stimulus for change.

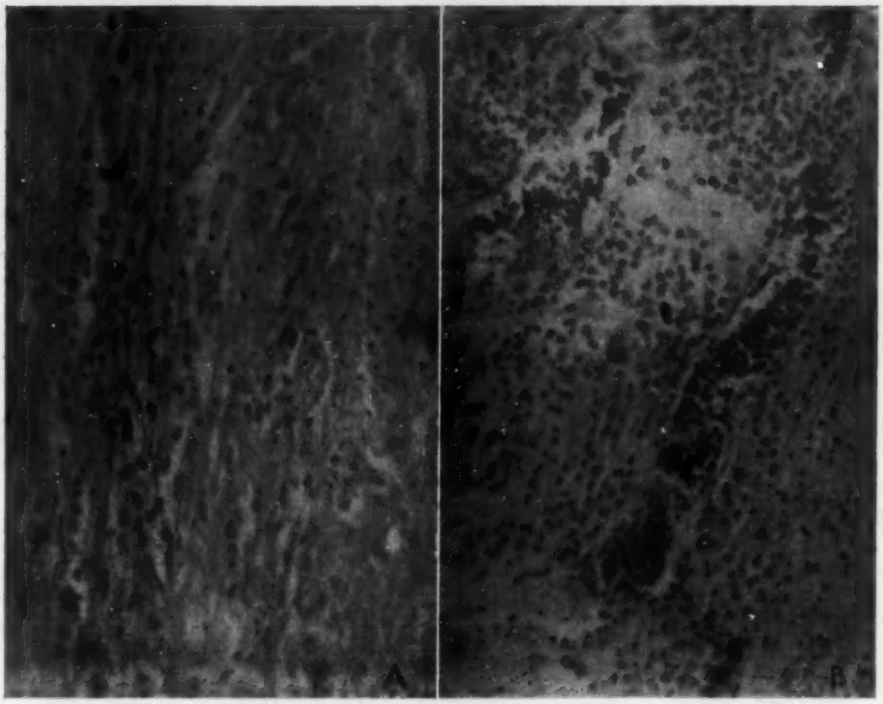

Fig. 8.—*A*, the cortex of a kidney ligated for seven weeks; *B*, for eight weeks. Helly fixation; hematoxylin-eosin-azure II; × 350.

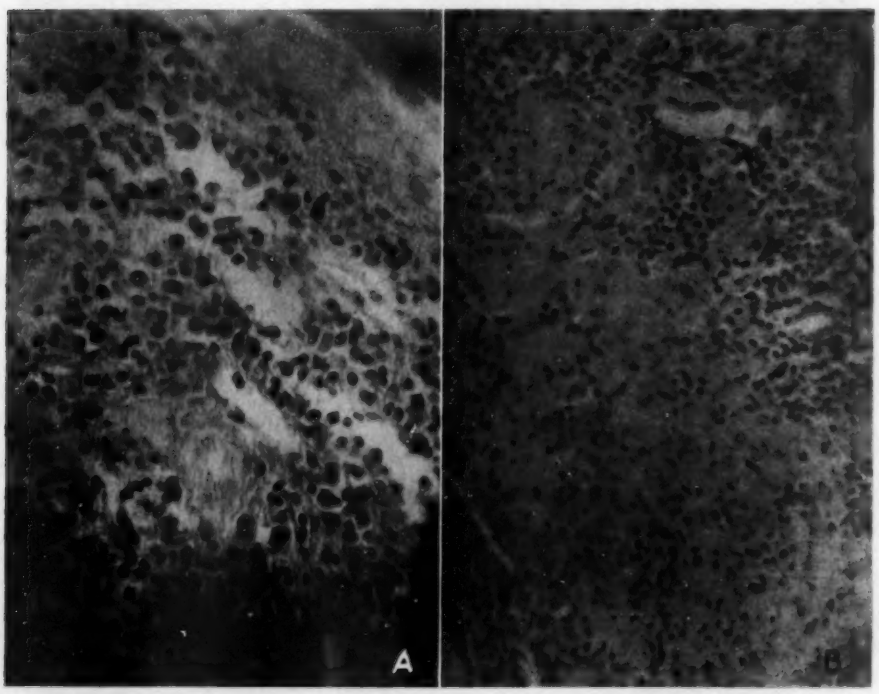

Fig. 9.—*A*, the cortex of a kidney ligated for nine weeks × 500; *B*, for nine weeks. Helly fixation; hematoxylin-eosin-azure II; × 350.

Beyond the four week stage, up to and including the ten week stage, most of the kidneys examined showed progressive fibrosis (figs. 8*A* to 9*B*), replacement of tubules, flooding of the fibrous tissue with lymphocytes, transition stages between small lymphocytes and plasma cells and large lymphocytes, and between plasma cells and Russell body cells. Russell body cells present in a kidney of eight weeks' ligation contained inclusions with great diversity of shape (fig. 10*A*). In contrast with the large eosinophil inclusions characteristic of the Russell body cells were the small eosinophil globules present in certain plasma cells (fig. 10*B*). This type of plasma cell in which the cytoplasm was filled with small eosinophil globules has been called the eosinophil plasma cell by Dubreuil and Favre.[12]

Although the majority of kidneys in the later weeks of ligation showed these changes, some of them remained completely unchanged as regards regenerative organization. The capsule was thin, the tubules were present occupying the same amount of space as in the unligated kidney, and the intertubular stroma remained unchanged. In such kidneys, some of the tubules were calcified and appeared as shiny eosinophil or basophil masses in the eosin-azure II preparations.

The third zone of the kidney affected by ligation was the medulla. This zone includes the papilla, as well as the medullary portion at its base. In the kidneys of the earlier stages of ligation, this region was merely a necrotic mass cut off from the rest of the kidney by the corticomedullary zone of neutrophil granulocytes. The remnants of the necrotic renal epithelium were visible within the meshes of the reticulum framework, but there was little or no replacement of these tubules by macrophages. Few neutrophil granulocytes were present in the blood spaces, and usually the whole medullary mass showed shrinkage after the first week. This shrinkage went steadily on until the tenth week; then the kidney was much smaller than its original size and the medulla occupied only a small central portion. As late as eight weeks following ligation, the necrotic medulla could be readily shelled out of the fibrous cortex on hardening. The fibrosis which took place in the cortex had apparently not invaded the medulla.

A series of experiments was made to see whether the extirpation of the spleen would have any effect on the changes in the ligated kidney. Kidneys from animals of this series showed no differences from those of the simple ligation, except possibly an increase in the amount of lymphoid tissue in the cortex.

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12. Dubreuil, G., and Favre, M.: Cellules plasmatiques. Plasmazellen à granulations spécifiques. Cellules à corps de Russell (cytologie et formes évolutives), Arch. d'anat. micr. **17**:302, 1921.

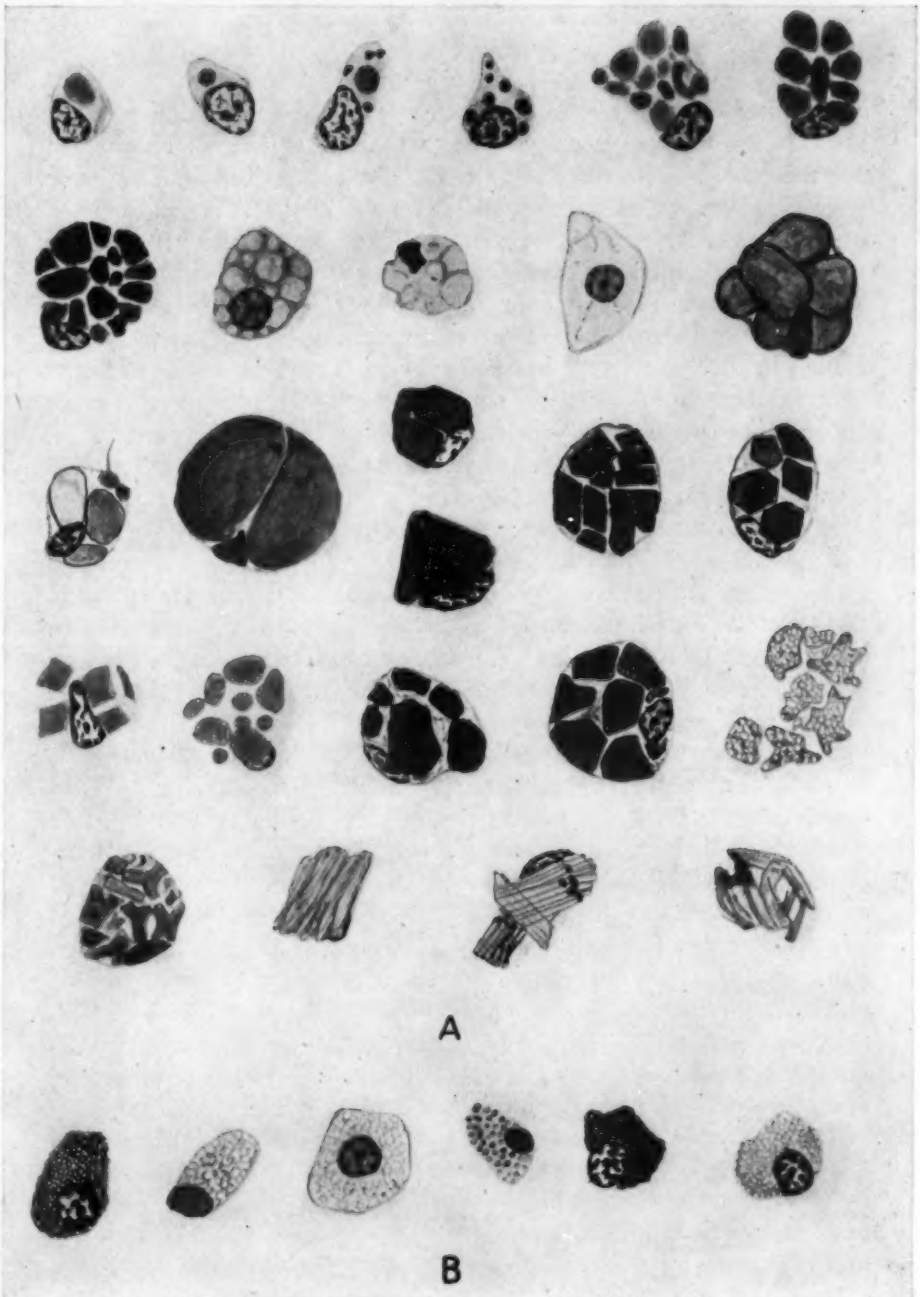

Fig. 10.—*A*, drawings of various types of Russell body cells from the cortex of a kidney ligated for eight weeks. The inclusions are eosinophil in reaction. The depth of the ink indicates the degree of tinctorial (red) reaction. *B*, drawings of plasma cells with eosinophil inclusions. Note uniformity of size and complete filling of cytoplasm with globules as compared with the arrangement of the inclusions of the Russell body cells. Helly fixation; hematoxylin-eosin-azure II; × 1,350.

COMMENT

In these experiments, we failed to find in the ligated kidney of the rat a series of changes comparable to those described by Maximow [7] for the rabbit. The changes most like those described by Maximow were those leading to the formation of bone in the subepithelial layer of the pelvis. However, no myeloid tissue accompanied this bone. Under no circumstances were small lymphocytes observed to change into hemoblasts. Since no areas of entrapped lymphocytes were found following ligation, all the lymphocytes occurring in the stroma of the kidney in the later stages of ligation were considered to be migrants from invading lymphatics. Stages between small lymphocytes and large lymphocytes were readily seen, as were transition stages between small lymphocytes and plasma cells. From the conditions found here it would seem that the plasma cells are degeneration phases of small lymphocytes. The plasma cells themselves become modified into Russell body cells and eosinophil plasma cells. From the shrunken appearance of the nuclei of the Russell body cells it is concluded that they are stages in the degeneration of plasma cells. Such a conclusion disagrees with the claim of Dubreuil and Favre,[12] who as a result of their observations on the Russell body cells in the omentum of the rabbit stated that the Russell body cells are possibly secretory cells of the rhagiocrin type. Our conclusion as to the degenerate nature of the Russell body cells is further strengthened by the sequence of events leading to their appearance in the cortex of the ligated kidneys, the general pyknotic character of their nuclei and the diversity in the shape of their inclusions. The inclusions appeared to be the result of the resorption of some substance from the surrounding tissue, which gradually increased in amount, and which was deposited in the cell in more or less crystalline form.

There was no evidence in our material for the view held by Maximow that some of the lymphocytes change into polyblasts. The cells that we call macrophages and consider comparable to the polyblasts of Maximow were all of extrarenal origin, either from monocytes or tissue macrophages. We are in agreement with the view of Maximow that the fibroblasts and macrophages are distinct entities, at any rate so far as they occur in ligated kidneys. From the earliest appearance of macrophages and fibroblasts, these two series of cells took distinct parts in the changes in the cortex of the ligated kidney. The fibroblasts extended between the tubules and deposited a collagenous matrix. The macrophages invaded the tubule remnants and digested them, thereafter remaining as occupants of the reticulum outlining the shape of the tubules.

The conditions that were present in the ligated kidney at the end of the first week were much like those in experimental lesions of the

liver of the rat as described by Higgins and Murphy.[13] The necrotic area was walled off by a zone of neutrophil granulocytes, outside of which was a layer of macrophages. Higgins and Murphy concluded that in the liver the macrophages arose from two sources: the agranulocytes of the blood stream and the local histiocytes of the periportal tissue including detached Kupffer cells. In later stages, the enclosing wall contained fibroblasts, which they concluded were transformed macrophages developed largely from Kupffer cells. In our material, the history was clear that the macrophages were entirely distinct from the fibroblasts throughout the whole experimental series. Beginning with the third day following ligation, the macrophages and fibroblasts invaded the kidney from the capsule. Each had its own function. The macrophages cleared away débris and replaced the tubule cells; the fibroblasts followed along the reticulum lined spaces and deposited collagenous fibers between the reticulum fibers. There was no evidence in our material that the macrophages had a later history comparable to that described by Higgins and Murphy for the lesions of the liver. Of particular interest was the border of polymorphonuclear granulocytes that persisted between the necrotic medulla and the cortex and the similar wall of such cells around the lesion in the liver. In the liver they lay first in the lesion and gradually cleared it to take up positions on the margin of the necrotic area, but in the kidney they hardly ever penetrated the medulla.

Following ligation in the rabbit's kidney most of the tubules of the cortex early became calcified (Maximow[7]). There was little calcification in the kidneys in our material. Any explanation of this difference in two apparently similarly constructed kidneys would be merely a guess, unless the chemical conditions accompanying the stages of ligation were available.

The experimental conditions established here following ligation compare with conditions of infarction in the human kidney. Morphologically, the cortex of the rat's kidney on ligation is invaded by one large infarct. The degree of repair and replacement of the renal tissue depends on the reactions of the surrounding structures, particularly the collateral circulation. Infarcts in the kidney of man are usually limited to isolated regions and are produced by emboli in the branches of the renal arcade. Also, it seems important to note that they are most frequently found in the cortex only, and there end centrally at the border of the cortex and medulla. This is exactly the relation of the infarct in the rat's kidney. In the case of the renal infarct of man, when replacement occurs the process is initiated by autolysis of the tubules, and the area of infarction is invaded by poly-

13. Higgins, G. M., and Murphy, G. T.: I. Experimentally Induced Localized Inflammatory Reactions in the Liver, Arch. Path. **9**:659, 1930.

morphonuclear granulocytes. According to Wells,[14] the leukocytes set free a substance called trephone which reacts on the surrounding tissues, particularly macrophages, fibroblasts, endothelium and lymphocytes. The initiation of such changes begins in the kidney of the rat following the third day of ligation. When the polymorphonuclear granulocytes begin to enter the kidney stroma, and after they have accumulated in large numbers at the corticomedullary boundary, the trephones presumably set free react on the other labile tissues and facilitate a gradual replacement of the whole mass by granulation tissue. The kidney gradually becomes smaller as the fibrous organization proceeds, so that by the end of the tenth week the kidneys are merely small fibrous, lymphoid masses.

Such an explanation of the replacement of the cortex by granulation tissue fails, however, to explain the persistence of the necrotic medulla. Why do the neutrophil granulocytes fail to penetrate the medulla? In answer, one might suggest that the autolytic process is not strong enough there to attract them. And if the neutrophil granulocytes do not enter the medulla, then the other elements that are considered to be influenced by the neutrophils do not progress beyond the corticomedullary boundary.

In addition to the cytologic changes in the kidney, we wish to call attention to the demonstration in our preparations of the renal basement membranes. In the normal kidney, stained with the Foot technic for the demonstration of reticulum, the reticulum fibers lining the intertubular capillaries are sharply evident (fig. 2*A*), but the homogeneous basement membrane shown by Mall[15] to be coexistent with the reticulum is not clear. However, after ligation for twenty-four hours or more, as long as tubular remnants persist, the homogeneous band that extends around the periphery of the tubules between the renal epithelium and the reticulum is conspicuous (fig. 5*B*). On necrosis of the tubules, the renal epithelial cells shrink away from the basement membrane, which in the Foot preparations appears as a pinkish band. This membrane also covers the surface of the glomerulus. The membrane persists for some time after necrosis of the tubules, indicating that it is of a nature different from the renal epithelial cells. From its reaction in the silver preparations counterstained with van Gieson's picric acid-acid fuchsin solution this membrane appears to be of a collagenous nature.

The study of the material by the method of supravital staining with neutral red and janus green was undertaken to see whether we could

14. Wells, H. G.: Chemical Pathology, ed. 5, Philadelphia, W. B. Saunders Company, 1925.

15. Mall, F. P.: Note on the Basement Membranes of the Tubules of the Kidney, Bull. Johns Hopkins Hosp. **2**:133, 1901.

discriminate between the globules of the macrophages and those of the Russell body cells. The globules were red, yellow or uncolored. Since these color differences mean merely differences in the hydrogen ion concentration, we could not make color discrimination between the globules of macrophages and Russell body cells. Many of the macrophages showed the characteristic petaloid pseudopodia. Engulfed materials, such as neutrophil granulocytes and effete red blood corpuscles, were more readily seen in the macrophages under supravital treatment than in the fixed material.

SUMMARY

Ligation of the major blood vessels of the kidney of the albino rat for a period of ten weeks is not followed by ectopic formation of bone-marrow.

Intramembranous bone may occur in the subepithelial connective tissue of the renal pelvis after four weeks' ligation.

The sequential pictures in the renal cortex following vasoligation are as follows: necrosis of renal tubules (in twenty-four hours); invasions of the cortex by neutrophil granulocytes from the capsular vasa (in three days); progressive replacement of the renal tubules by macrophages (in from one to ten weeks); progressive replacement of the renal capillaries by fibroblasts and collagenous tissue (in from one to ten weeks); persistence of the endothelial reticulum for eight weeks until completely obliterated by collagenous fibers; invasion of the fibrous neocortex by blood vessels (beginning at one week); invasion of the neocortex by lymphatics (beginning with the third week); migration into the fibrous neocortex of small lymphocytes and their metamorphosis into large lymphocytes and plasma cells (beginning with the third week); degeneration of plasma cells into Russell body cells (beginning with the fourth week), and isolation of the medulla from the cortex by a corticomedullary zone of neutrophil granulocytes (beginning with the first week).

Splenectomy synchronous with vasoligation does not effect changes different from those caused by simple ligation.

Kidneys into which trypan blue is injected before ligation show changes similar to those following simple ligation.

The renal intertubular capillary system is lined with a reticulum membrane that is separated from the renal epithelium by a homogeneous basement membrane, possibly collagenous. This membrane is more resistant to necrosis than the renal epithelial cells.

HUMAN URETER WITH STRIATED MUSCLE AND CILIATED EPITHELIUM *

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In order to amplify the slide collection used by students engaged in the study of normal histology, a resident pathologist of the Philadelphia General Hospital, at our request, excised about an inch of a grossly normal ureter from a recently dead adult cadaver and placed it in formaldehyde fixative. As he supposed that the material was to be used for histologic purposes only and that its freshness and good fixation were matters of prime importance, no memorandum was made by which it was subsequently possible to identify the body from which the tissue was removed, nor can the pathologist, who collected various tissues for various persons and for various purposes that same afternoon, now remember. The routine histologic studies of the necropsy material of about that date have not, however, revealed other anomalies.

The fragment of ureter, having been duly sectioned, proved to be exceptionally interesting in that it presented an anomaly of histologic structure that, so far as we have been able to determine, has not heretofore been observed. Indeed, a careful examination of the literature has failed to discover any mention of histologic anomalies of the ureter.

OBSERVATIONS

The Muscular Coats.—There was a complete absence of the usual (normal?) unstriated muscle, its place being taken by perfectly striated fibers. These were arranged in three separate layers: (1) an inner layer, composed of fibrillar connective tissue and a few muscle fibers, in which the direction of the fibers was uncertain, different fasciculi seeming to run in different directions, mostly obliquely, though rather circumferentially than longitudinally; (2) a middle layer, circumferential in disposition, and made up of beautiful parallel fibers, of which the transverse striations and peripheral nuclei were distinct, and (3) an outer layer of longitudinal fibers, also of the striated variety.

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* From the McManes Laboratory of Pathology, University of Pennsylvania, and the Woman's Medical College of Pennsylvania.

Fig. 1.—Section showing the entire thickness of the ureter with all of its coats. The inked oblong shows the field selected for the higher magnification shown in the next illustration.

Fig. 2.—The cross-striations and peripheral nuclei are typical of the muscle tissue in this peculiar ureter.

It may be seen that the distribution and arrangement of the layers were unusual, and if Kölliker is right that the middle coat occurs only near the bladder, it may be assumed that the portion of the ureter examined must have been taken from the lower part of its course.

The Mucosa.—The epithelial lining was composed of stratified squamous cells unlike the normal urothelium. There was a distinct basal layer surmounted by from half a dozen to a dozen layers of cells, which, like those of the mucosa of the mouth, gradually flattened into

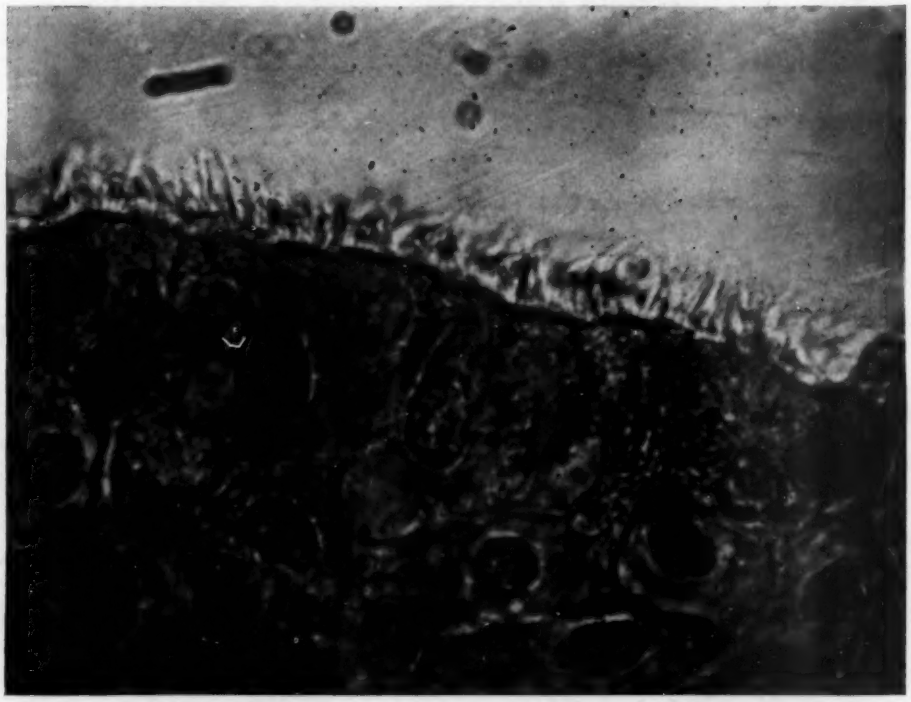

Fig. 3.—High power magnification of islet of ciliated columnar epithelium in the lining of the ureter.

scales that desquamated. But there were exceptions, for in many places, usually of limited extent, the cells did not flatten, but after passing upward through a varying number of successive layers of polyhedral cells with pale cytoplasm, unexpectedly turned into columnar cells with ovoid nuclei at the bases, highly polychromatophilic cytoplasm and perfectly formed long cilia.

The discontinuousness of the columnar epithelium was interesting. As the section was moved on the stage of the microscope so as to follow the wavy line of the rugose mucosa, a long stretch with flattening cells

was suddenly interrupted by a group of perhaps a half dozen ciliated columnar cells, then another long stretch, with flattened cells, and then again a dozen or more ciliated columnar cells, and so on.

The photomicrographs accompanying this brief report show what has been described.

The explanation of the anomaly is extremely difficult. Suppose that in early embryonal life the ureters instead of having budded from the sides of the urogenital sinus, as they usually do, started at about the point of insertion of the wolffian ducts, as they frequently do, or from the lower part of the wolffian ducts themselves, as it is thought that they may do, then it is conceivable that in their upward extension they may have carried enough cells of the wolffian ducts for these to have survived the embryonal period and to have descendants even into adult life.

But our attempts to explain the presence of the striated muscle in the wall of this ureter have failed because our acquaintance with embryology is inadequate to furnish any clue.

FETAL ADENOMA OF THE HYPOPHYSIS AND DERMOID CYST OF THE HYPOTHALAMUS*

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The hypophysis and the adjacent tissues are the site of a great variety of tumors. The hypophysis itself is composed of several elements, and each is the potential anlage of a separate type of neoplasm. The pars nervosa gives rise to gliomas and the pars glandularis to simple hyperplasias, adenomas and carcinomas of many kinds. Even the dubious pars intermedia has been credited with certain tumors. Each of the cellular elements in the pars anterior has its special prototype in neoplasms. Thus, hypophyseal tumors have been described, composed entirely or chiefly of eosinophil cells, basophil cells, principal cells, "transitional cells" (Kraus [1]), pregnancy cells and rarely even fetal indifferent cells. All possible combinations of these cells may be seen in the mixed adenomas, and in a single hypophysis two or more varieties of these tumors may be separately found. The relative frequency of the various types of tumor is roughly proportional to the relative numbers of the type cells. Thus, eosinophil adenomas are the most common, fetal cell adenomas are very rare, and pars intermedia tumors practically never occur in man.[2]

The tissues adjacent to the hypophysis are also the apex of several embryologic infoldings which leave behind them congenital rests of all kinds. Each such rest retains part or all of the potentialities of embryonal cells and may subsequently differentiate into tumors of the greatest variety and complexity of structure. These vary all the way from simple squamous epithelial cysts to teratomas and even to double monsters.

Besides the inclusion tumors from oral epithelium or external epithelium, other tumors, such as those that may be found elsewhere in the brain, may also appear in the hypophyseal area. These may be endotheliomas from the meninges, gliomas and neurocytomas from the cerebral substance or papillomas from the choroid plexus of the third

* Submitted for publication, June 30, 1930.

* From the Department of Pathology of the Cook County Hospital.

1. Kraus, E. J.: Die Beziehungen der Zellen des Vorderlappens der menschlichen Hypophyse zu einander unter normalen Verhaeltnissen und in Tumoren, Beitr. z. path. Anat. u. z. allg. Path. **58**:159, 1914.

2. Kraus, E. J., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1926, vol. 8.

ventricle. In this area, even these tumors, however, acquire a special significance beyond that which they possess in other parts of the brain. They assume special pressure relationships to the cranial nerves, particularly the optic nerve. The hypophysis and the hypothalamus are centers for the physiologic control of many important visceral functions. Tumors in this region, by destroying one structure or another, produce specific depletion symptoms and permit some insight into the special functions of the various parts of the hypophyseal area.

In the course of autopsy at the Cook County Hospital on two clinically obscure cases, two unusual types of tumor of this region were found. One was a rare tumor of the hypophysis itself. The other belonged to the group of inclusion tumors of the hypophyseal region and apparently was responsible for certain disturbances in visceral functions. The description of these cases is warranted as a matter not so much of recording rare tumors, as of calling attention to several much mooted problems in the anatomy, embryology and pathology of this area.

REPORT OF CASES

CASE 1.—*Clinical History.*—Late one evening, a poorly nourished white man, 46 years old, was admitted to the neurology service. He was extremely ill and semistuporous, so that his history was obtained from him with difficulty. For two years he had been suffering from intermittent attacks of dull, aching pain in the right hypochondrium. There had been considerable vomiting, and he had lost 70 pounds (31.8 Kg.) in weight. In the last three days, he had suddenly found himself getting stiff in both upper and both lower extremities. He was soon unable to walk because of the marked spasticity.

Physical Examination.—Heart, lungs and abdomen were normal, except for tenderness in the right hypochondrium. There was poor visual acuity. The pupils were equal and regular, but reacted sluggishly to light and in accommodation. The cranial nerves were normal. The abdominal reflexes were absent. The knee jerk was absent on the left side, but exaggerated on the right. No pathologic reflexes were obtained. Sensation was dulled over the entire body, and the patient's mentality was clouded. Lumbar puncture yielded a cerebrospinal fluid that was clear and normal.

Diagnosis.—The patient died early the next morning, less than twelve hours after admission. It was impossible to make a definite diagnosis in this brief time, but it was ventured as: carcinoma of the stomach with recent cerebral metastases.

Postmortem Examination (by Dr. R. H. Jaffé).—At autopsy, the cause of the abdominal distress was found in a chronic peptic ulcer of the stomach, with marked stenosis of the pylorus. The stomach was markedly dilated with about 1,500 cc. of fluid. Its mucosa showed distinct rugae, the "état mamelonné" of chronic gastritis. The pylorus was the site of an oval ulcer, 7 by 3 mm. in diameter, with a smooth floor and sloping edges. The adjacent mucosa was pulled in toward it in the form of a healing, contracting scar. The pyloric ring was narrowed so that it had a lumen of only 8 mm. Supporting the suspicion of death in alkalosis were heavy calcium deposits in the tubular epithelium of the kidneys. No calcium was found, however, in any of the other tissues.

In removing the brain, the hypophysis was seen to bulge from the sella into the interpeduncular space. It was covered on its superior aspect by the tightly stretched operculum sellae. The hypophysis could be easily peeled out of the sella, and it was surrounded by an intact capsule. It was 30 mm. in transverse, 23 mm. in anteroposterior, and 22 mm. in longitudinal diameter. The sella itself was wide and flat, 32 by 25 mm. in diameter and 10 mm. deep. Its internal surface showed no erosion.

The optic chiasma did not seem to be affected by the bulging of the hypophysis. The tracts were of normal size, shape and structure. Neither the peduncles

Fig. 1.—Compressed tissue of the anterior lobe, forming a thin, fibrotic capsule for the tumor. Leitz obj.; 8 mm. apochromatic lens; periplanar 4.

nor the tuber cinereum were involved. The internal carotid arteries, especially the right, were somewhat compressed by the enlarged hypophysis, but could be easily separated from it.

A saggital section through the hypophysis exposed a smooth, homogeneous, light grayish-brown surface with distinct blood vessels and several small, light orange-yellow patches. Underneath the capsule, also, there were several light gray, slightly transparent areas from 1 to 2 mm. in diameter. The whole mass was soft and occupied almost the entire substance of the hypophysis, except for the thin capsule. The infundibulum appeared attached to the center of it.

The brain itself weighed 1,315 Gm. The leptomeninges at the base, especially about the oculomotor nerves, were slightly thickened with whitish lines. The leptomeninges over the convexity were smooth and transparent.

In addition, there were found parenchymatous degeneration of the myocardium, with dilatation of all the cardiac chambers, brown atrophy of the liver and passive congestion of the spleen.

Microscopic Examination.—The posterior lobe of the hypophysis was well preserved and showed no marked deviation from its normal microscopic appear-

Fig. 2.—Compressed zona intermedia of the anterior lobe, forming the posterior part of the capsule of the tumor. Leitz obj.; 8 mm. apochromatic lens; periplanar 4.

ance. The anterior lobe was expanded to a thin shell which formed a capsule for the main mass of tissue occupying the gland (fig. 1). This capsule contained all the elements of the normal anterior lobe, but its cells were compressed and arranged in parallel cords separated by strands of fibrillar connective tissue. Small groups of basophil cells predominated, but there were also cords of principal cells and single eosinophil cells. Posteriorly, adjacent to the pars nervosa, this capsule contained all the remnants of the normal intermediate or boundary zone of the hypophysis. There were colloid-filled follicles lined by low cuboidal or flat epithelium and cords of principal cells, among which were scattered occa-

sional basophil cells. With all stains used, the colloid in these follicles was identical with that found in the main mass of the gland.

The main part of the hypophysis, the light gray-brown central mass, was composed of long and slender columnar cells, which were arranged radially about the blood vessels and connective tissue septums. On tangential sections, they appeared in palisade arrangement. Each cell had a delicate, finely granular cytoplasm and an oval nucleus occupying the central part of the cell. The chromatin formed fine granules and was evenly distributed within the nucleus. There were

Fig. 3.—Low power view of fetal cell adenoma in the midportion of the anterior lobe, showing the characteristic palisade arrangement. Frozen section; Leitz obj.; 8 mm. apochromatic lens; periplanar 4.

fine lipoid granules in the cytoplasm immediately about the nucleus. Wedged in between these cells, there were single small cells with deeply stained nuclei. There were also numerous large cells with an ample cytoplasm, which was filled by large fat droplets and by numerous hyaline droplets. The nuclei of these cells stained deeply and were often crenated.

Between the rings of columnar cells and the blood vessels were often spaces filled by a homogeneous, oxyphil, colloid-like material. This material at times was vacuolated. In it were suspended isolated nuclei resembling those of the

perivascular cells, as well as whole cells with vacuolated cytoplasm containing hyaline droplets. Throughout the tumor, but most numerous near the surface, were follicles and even small cysts up to 2 mm. in diameter. They were filled by material similar to that described as occurring about the blood vessels and were lined by low cuboidal cells, so that they resembled the colloid-filled follicles of the thyroid gland.

With hematoxylin and eosin, this colloid stained pink; with Mallory's stain, either a deep blue or a light orange-yellow. With Kraus' polychrome methylene-

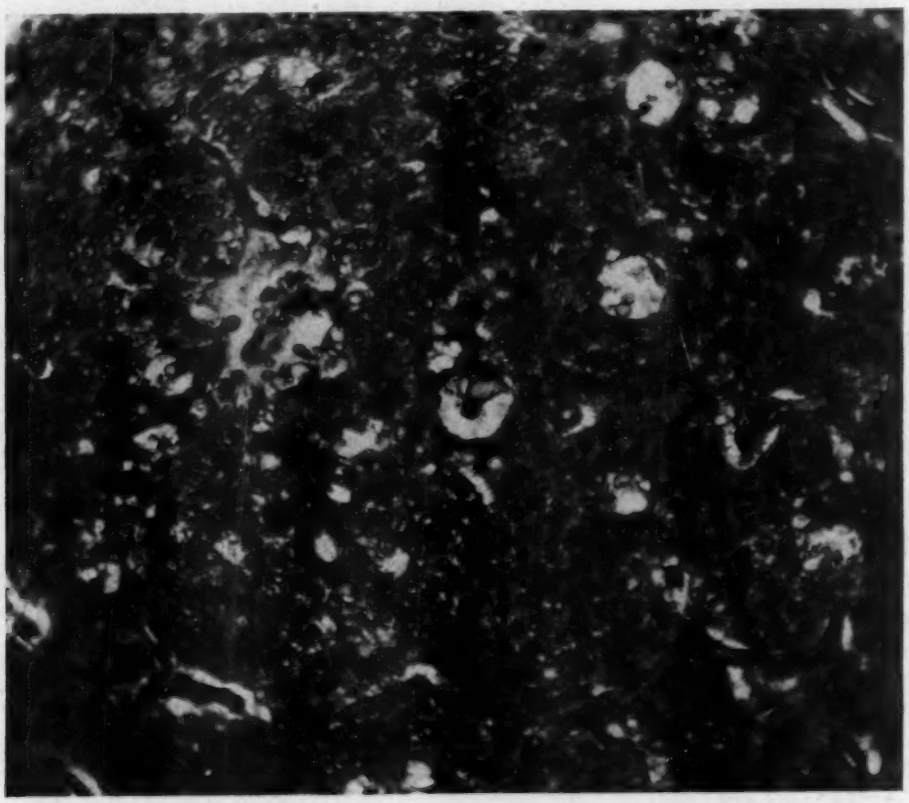

Fig. 4.—High power view of fetal cell adenoma in the midportion of the anterior lobe, showing the characteristic columnar cells, with intracellular and extracellular colloid droplets and the formation of colloid-filled spaces. Paraffin section; Leitz obj.; 4 mm. apochromatic lens; periplanar 4.

blue-acid fuchsin-tannic acid stain,[3] most of the colloid was light blue (fuchsinophobe). Fuchsinophil (red) and tannic acid-fast (violet) colloid were, however, also present. The origin of this colloid could readily be followed from droplets within the fetal cells. For, with each stain used, the same staining reaction was

3. Kraus, E. J.: Das Kolloid der Schilddruese und Hypophyse des Menschen, Virchows Arch. f. path. Anat. **218**:107, 1914.

seen in the droplets within the fetal cells as was found in the adjacent colloid masses. Sometimes the entire cytoplasm of one or of several cells was transformed into the same homogeneous material. The colloid droplets could then be seen between the fetal cells and finally, in similar staining reaction, were gathered in the perivascular spaces and larger cysts.

With the sudan III stain, fine fat droplets were similarly seen in the cytoplasm of the cells, then between the cells and, finally, within the colloid-filled spaces. They appeared in these spaces in the form of free clusters and also within desquamated cells, but there were no "spheroids."

Anatomic Diagnosis.—The anatomic diagnosis was: fetal adenoma arising from the midportion of the anterior lobe of the hypophysis; healing chronic peptic ulcer of the stomach, with stenosis of the pylorus and marked gastric dilatation; calcium deposit in the renal tubular epithelium, and parenchymatous degeneration of the myocardium.

CASE 2.—*Clinical History.*—A colored woman, 36 years old, was admitted to the hospital in a semistuporous condition, from which she could not be roused. A history was obtained from relatives to the effect that for two years she had been suffering from frequent and severe headaches. She had taken to drinking large quantities of water. There was a consequent polyuria, especially nocturnally, but no loss of weight.

For the last five months, her vision had been failing progressively, and her headaches had begun to be more frequent and severe. In the last two weeks, she was oppressed with marked somnolence and slept almost constantly. Two days before admission, she became irrational and finally lapsed into deep stupor.

Physical Examination.—The patient was rather well nourished and had a normal temperature and blood pressure, but a pulse rate of only 60. The pupils were irregular and dilated and did not react to light. The fundi were normal, except for a slight hyperemia of the disks. No papilledema was found. The results of physical and neurologic examination were otherwise negative.

One drop of urine reduced 5 cc. of Haines' solution. The urine was loaded also with albumin and contained a few hyaline casts. The blood chemistry showed a normal urea nitrogen. This excluded the possibility of uremic coma. The dextrose content of the blood returned a reading of 272 mg. per hundred cubic centimeters. After one injection of 40 units of insulin, the blood sugar dropped to 70, and the glycosuria disappeared. Still the patient remained in coma, so that the diabetes could not have been its cause. A syphilitic basilar meningitis was also finally considered, but the Kahn reaction was negative. The patient died in less than twenty-four hours after entrance, before anything more could be done to clarify the diagnosis. Cerebrospinal fluid for a Wassermann reaction was not taken.

Postmortem Examination.—Autopsy disclosed the essential pathologic changes in the brain. It weighed 1,000 Gm. Its convolutions were flattened. The right hemisphere was distinctly larger than the left, so that its transverse diameter was 8 cm., as compared with 6 cm. for the left. The longitudinal diameter of both hemispheres was 17 cm. At the base of the brain, the space between the optic chiasma and the infundibulum was the site of a lobulated, cystic, light grayish-brown mass, 3 cm. in diameter. It compressed the optic tracts, especially the left, the outlines of which were almost completely obscured. The right optic tract crossed the posterior third of the mass. Anteriorly and laterally, it was flanked by the anterior cerebral arteries. The anterior portion of the infun-

dibulum formed part of the mass, and the stalk of the hypophysis originated from its inferior aspect.

Coronal section through the mass revealed a cyst, 2.5 by 2.5 by 2 cm. in diameter, occupying the right subthalamic region and extending into and replacing the infundibulum. Its center was to the right of the median line. It did not displace the hypophysis or its stalk. Dorsally and anteriorly, the cyst was bordered by the anterior commissure. It was filled by a thick, light yellowish-gray fluid. It was lined by a wall that averaged 2 mm. in thickness. The wall was firm and dark reddish-brown, and contained several pinpoint-sized, hard, whitish deposits. The adjacent brain tissue was transformed into a soft, colloid-like substance.

The septum pellucidum was swollen and softened and contained numerous pinhead-sized, dark red patches. Similar areas were found in the lining of the

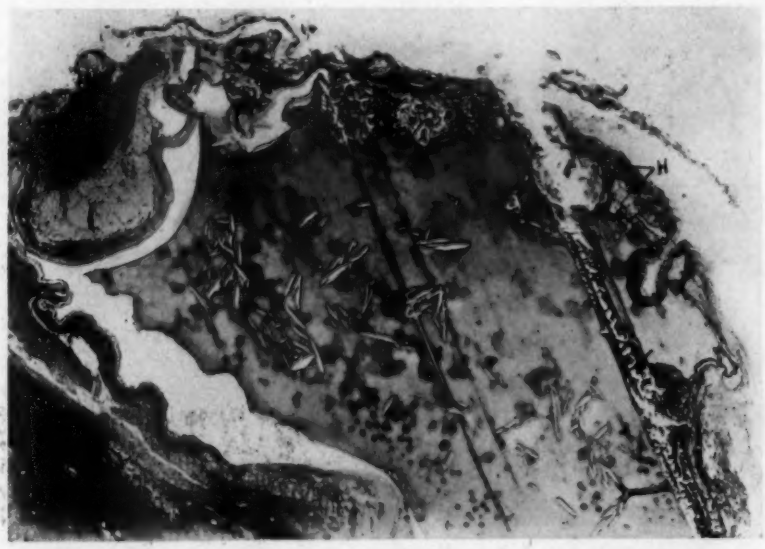

Fig. 5.—Low power view of a dermoid cyst of the right hypothalamus. Note the homogeneous content of the cyst, with fatty acid needles, the hornified pearls of squamous epithelium, the cartilage, the bone and the fetal hair structures (H), in the wall, with colloid degeneration and glia reaction in the adjacent brain tissue.

anterior horns of the lateral ventricles and in the anterior half of the corpus callosum. The lateral ventricles, especially the right, and the third ventricle were compressed; their lining was smooth.

As incidental observations, there were also chronic peptic ulcer of the stomach, bilateral salpingitis isthmica nodosa, syphilitis aortitis, brown atrophy of the heart and terminal bronchopneumonia.

Microscopic Examination.—Tumor mass in region of infundibulum: About the cyst was a wall of dense fibrillar connective tissue which was loosely and, in circumscribed areas, densely infiltrated by lymphocytes. It also contained small deposits of hemosiderin. The inside of this wall was lined by several layers of squamous epithelium with a distinct basal layer of cuboidal cells. The inner-

most layer of squamous cells appeared loosened and in places was desquamated. The cyst was filled by a homogeneous substance with many fatty acid needles and remnants of degenerated squamous epithelial cells.

The wall contained also numerous whirls and clusters of hornified epithelial cells, in which keratohyaline granules could be demonstrated (method of Weigert). Foreign body giant cells were seen about the hornified masses. Here and there, one could find structures resembling fetal hair follicles.[4]

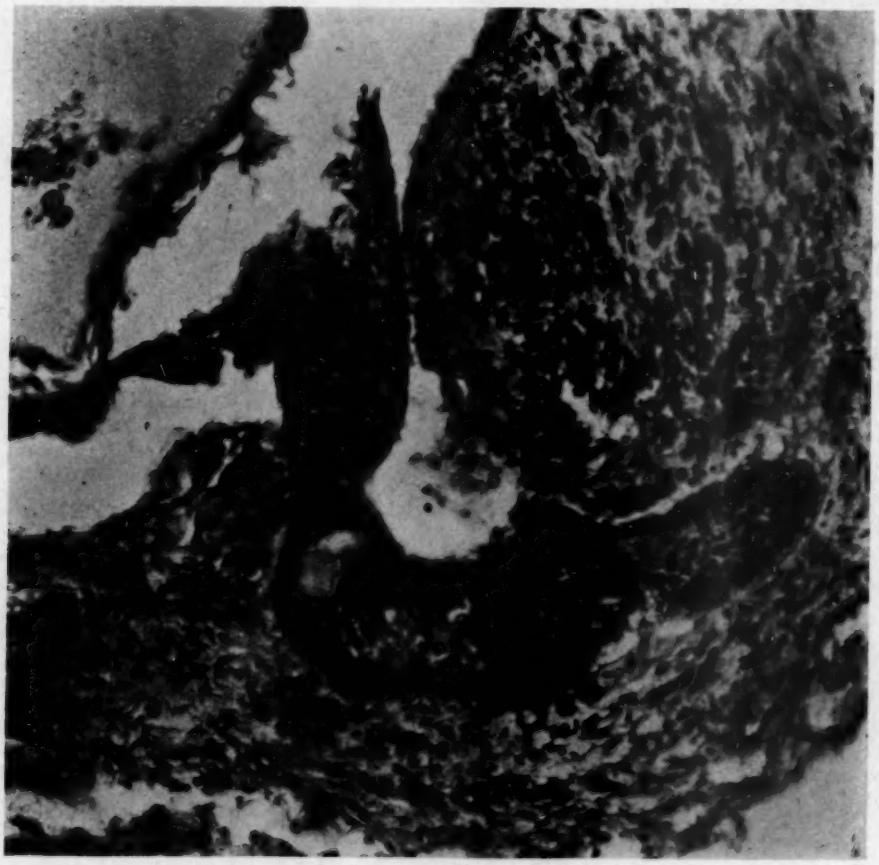

Fig. 6.—A fetal hair follicle in the wall of the cyst. Leitz obj.; 8 mm. apochromatic lens; periplanar 4.

There were also areas composed of numerous wide capillaries and scanty cellular stroma. Groups of coarse, irregular bone trabeculae with distinct osteoblasts were present. Adjacent to the bone there were small groups of lightly stained cuboidal cells with distinct membranes, uniformly vacuolated cytoplasm and round vesicular nuclei resembling embryonic fat cells.[5]

4. They were identical with the embryonic hair structures pictured by Fischel, A.: Entwickelung des Menschen, Berlin, Julius Springer, 1929, p. 562.

5. Fischel (footnote 4, p. 559).

The fibrous tissue capsule about the cyst wall was surrounded in turn by a proliferation of fibrillar glia and microglia cells. At the base, the glia tissue was scanty; laterally and dorsally it was more abundant and passed into the brain tissue. In places, the glia tissue broke down into a homogeneous mass in which scanty and tortuous fibrils were distinguishable. About the cerebral vessels adjacent to the broken-down tissue there were "cuffs" of lymphocytes.

Sections from the parietal cortex showed the changes characteristic of dementia paralytica in the form of perivascular round cell infiltrations of the leptomeninges

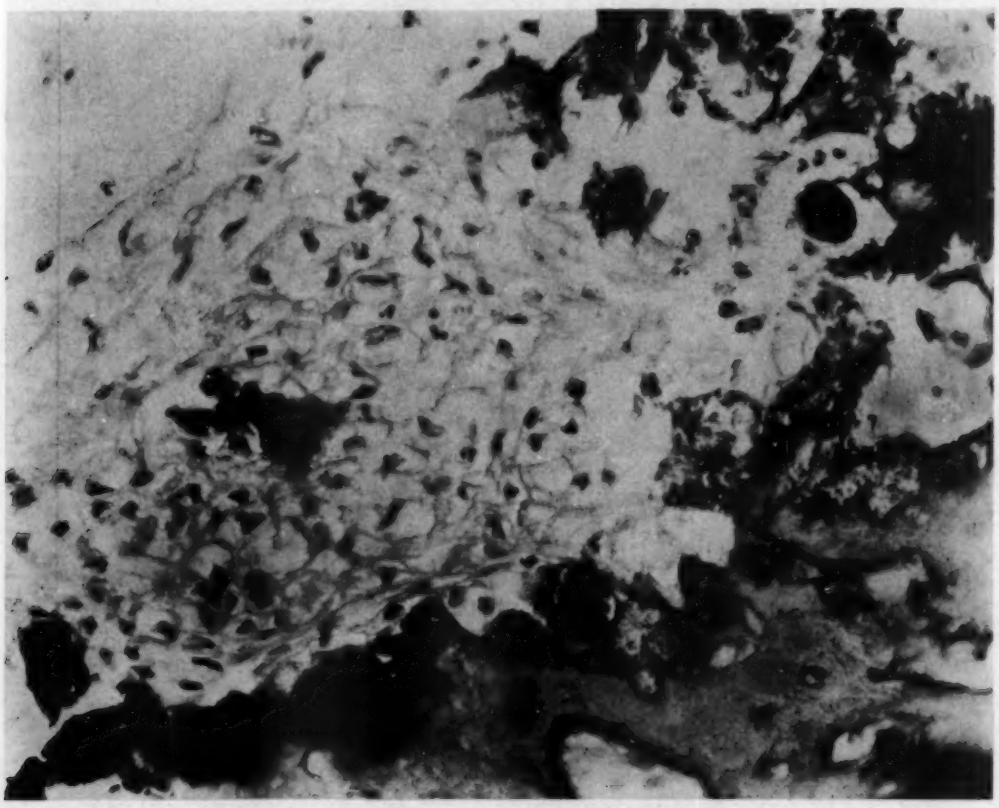

Fig. 7.—A group of embryonic fat cells in the wall of the cyst. Note the vesicular nuclei and the regular vacuolation of the cytoplasm. Leitz obj.; 4 mm. apochromatic lens; periplanar 4.

and the cortex, with degeneration and rarefaction of the ganglion cells and adventitial iron deposition.

The hypophysis was slightly excavated by the tumor mass. Its structure was well preserved, however, except for an increase of the interstitial tissue, which in places formed islands up to 1 mm. in diameter. Among the cells of the anterior lobe, the basophil elements predominated. The posterior lobe was apparently unchanged.

Anatomic Diagnosis.—The anatomic diagnosis was: dermoid cyst of the brain occupying the right hypothalamic region and the infundibulum; colloid degeneration of the adjacent brain tissue; hemorrhages and softening of the septum pellucidum and the anterior half of the corpus callosum; complete atrophy of the left, and partial atrophy of the right, optic tract; syphilitic aortitis; terminal bronchopneumonia, and paretic meningo-encephalitis.

COMMENT

The tumor described in the first case was probably an incidental observation. The entire clinical picture could be well accounted for on the basis of the peptic ulcer with pyloric stenosis, gastric dilatation and alkalosis. The tumor may have been a factor in the patient's death, but the brief clinical study precludes any definite statement to this effect.

It was apparently an adenoma of the hypophysis. It was not a simple hyperplasia, because it was definitely encapsulated. It was not a carcinoma, because it showed a definite alveolar arrangement, with no anaplasia, no infiltration, no erosion of the sella and no metastases.

It was an adenoma, but of rather an odd type. Its cells did not recall any of the chromophobe or chromophil elements of the pars anterior of the adult gland. Neither did they look like transitional cells or pregnancy cells. The high columnar cells in palisade arrangement, were strikingly different from any of these cell types. They did, however, resemble another type, namely, the indifferent cell of the fetal hypophysis. The whole adenoma tissue recalled the pars glandularis of a fetal hypophysis.

In 16 mm. embryos, the simple hypophyseal sac pinched off from its connection with the craniopharyngeal duct is lined uniformly by a simple layer of high cylindric epithelium. The posterior wall in contact with the pars nervosa is relatively stationary in growth. In the anterior wall there is a rapid proliferation to form a mass of columnar cells; this mass bulges forward and then curls laterally to enclose the pars posterior with an incomplete ring of glandular tissue. The pars anterior of the hypophysis in the third month of fetal life is composed almost entirely of these same high cylindric cells, arranged radially about the blood vessels and connective tissue septums like palisades (Kraus [2]). These cells, like those found in the adenoma, have a delicate, finely granular cytoplasm, and oval centrally placed nuclei with a finely granular, evenly distributed chromatin.

Rapidly, these undifferentiated fetal cells begin to mature. From them the entire structure of the adenohypophysis differentiates. Eosinophil cells are first developed. Then basophil cells appear and finally principal cells. The undifferentiated cells are in part slowly replaced

by differentiated ones, and the rest are further submerged by the rapid proliferation of the more mature elements. By the fifth month, they are reduced to a small proportion of the gland. At birth, relatively few are present. But even then, and at all ages throughout life, small groups of these undifferentiated columnar cells may be seen scattered among the differentiated elements (Cooper [6]). They are found in the lining of the vesicles in the intermediate zone and as isolated groups throughout the substance of the anterior lobe, especially in its lateral parts.

It is generally conceived that the differentiated cells can perpetuate themselves in cycles, with reversible transitions from one type to another. But these fetal cells are a constant source for new series of differentiations into principal cells, eosinophil cells, basophil cells, etc. Until at least early middle age, new series are being constantly started from them (Loewenstein [7]). These embryonal cell rests, in keeping with Cohnheim's theory, may thus be the indirect origin of adenomas of any differentiated cell type, which mature as they grow, or may directly originate an adenoma of undifferentiated fetal cell type.

The number of reported cases of fetal cell adenoma is small. As scanty as are fetal cells among the mature elements of the adult hypophysis, so infrequent are the fetal cell adenomas in comparison with the mature cell adenomas of the hypophysis. Loewenstein described a case of alveolar fetal cell adenoma. Kraus [1] presented a study of twenty-five cases of adenoma of the hypophysis. They included every possible variety and combination of hypophyseal adenoma, together with two cases of fetal cell tumor. One was a malignant fetal cell adenoma, and in the same gland an area of chief cell hyperplasia, as well as another area of simple fetal cell hyperplasia, were also found. The other was an adenoma-like fetal cell hyperplasia. These tumors usually begin after the age of thirty, when the differentiation of fetal cells into mature cells stops. Kraus was able to find transitions from fetal cells to principal cells in his cases. None was found in my case of fetal cell adenoma. All the cells were of the long, columnar, undifferentiated, fetal type.

They were arranged in columns and in palisades about the blood vessels. Often between them and the vessels were colloid-filled spaces. Colloid-filled follicles and even small cysts were formed, especially just beneath the capsule. The colloid was a prominent feature of the

6. Cooper, E.: Histology of Human Endocrine Organs at Various Ages, New York, Oxford University Press, 1925.

7. Loewenstein, C.: Die Entwickelung der Hypophyse Adenome, Virchows Arch. f. path. Anat. **188**:44, 1907.

microscopic sections. The cysts could even be seen by the naked eye, just as they may often be seen in the intermediate zone of the normal hypophysis bordering the posterior lobe. There are three possibilities for the origin of hypophyseal colloid. It may be a product of active secretion by differentiated cells of various kinds. Some hold that there is a different secretion from each type of cell, and there is good clinical evidence to support this view. Others hold that all the mature cell types are but successive stages in a single secretory process. The colloid may also be the product of degeneration of differentiated or of undifferentiated cells. Finally, it may appear as a vestige of the old external secretion, a fruitless secretion, within the pinched-off daughter cysts of Rathke's pouch.[8] In the adult gland, all three possibilities may be realized, but how to distinguish the three types of colloid is a difficult matter.

Only part of the colloid-filled follicles were lined by the cells of Rathke's pouch. The rest were lined wholly or in part by differentiated cells of all kinds, with only an occasional undifferentiated cell. One could trace the origin of each type of colloid from the substance of the adjacent cells, but here differentiation ended. Iodine was never found in appreciable amounts in any of these three types of colloid, except when therapeutically administered, so that there were no means of chemical identification.[9] Beyond reasonable doubt, the anterior lobe of the hypophysis has an internal secretion, but it is probably not stored to any great extent within the colloid masses. Most of the secretory colloid is probably unloaded directly into the blood stream (Maurer,[10] Rasmussen[11]). Kraus concluded that most of the colloid as it is found in the adult gland is not the product of an active secretion, like that of the thyroid gland, and not a stored vestige of the old external secretion, but is a product of cellular degeneration.

Morphologic evidence is not enough to establish definitely physiologic qualities, but it, at least, indicated that the colloid seen in the fetal adenoma arose also, most probably, by cellular degeneration. The perivascular colloid accumulations had no resemblance to the vesicles of

8. Erdheim, J.: Ueber Hypophysentumoren, Wien. med. Wchnschr. **74**:425, 1924.

9. Wells, H. G.: Chemical Pathology, Philadelphia, W. B. Saunders Company, 1925.

10. Maurer, C., and Lewis, D.: The Structure and Differentiation of the Specific Cellular Elements of Pars Intermedia of the Hypophysis of the Domestic Pig, J. Exper. Med. **36**:141, 1922.

11. Rasmussen, A. T.: Histological Evidences of Colloid Absorption Directly by Blood Vessels of the Human Hypophysis, Quart. J. Exper. Physiol. **17**:149, 1927.

Rathke's pouch. It was not readily conceivable that the undifferentiated fetal cells would be elaborating, as yet, any active secretion. Cells in the course of degeneration could be seen among the intact ones, and desquamated degenerated cells were found suspended within the colloid. The observations in the fat stains also bespoke a degenerative origin for this colloid, because "spheroids" such as those seen in the thyroid gland as marks of its secretory activity were altogether absent (Jaffé,[12] Kraus.[13]).

In the normal gland, this formation of colloid is most active in the posterior part of the anterior lobe, adjacent to the pars nervosa. Here are also found the vesicles derived from Rathke's pouch. Numerous colloid cysts and follicles therefore characterize this intermediate or boundary zone ("Markschicht"), or cyst zone, of the anterior lobe. They distinguish it from the posterior lobe behind, and the rest of the anterior lobe in front. This and its position have caused a frequent confusion of the intermediate zone of man with the colloid-bearing pars intermedia seen in lower animals.

In animals such as the pig, calf, cat, rat, dog, frog, woodchuck, opossum, etc., the hypophysis presents a well developed pars intermedia with characteristic histologic structure and presumably a specific function.[14] It lies between the hypophyseal cleft and the pars posterior. It is derived by a special line of differentiation from the columnar cells of the posterior walls of Rathke's pouch, just as the pars anterior is derived by another line of differentiation from the anterior wall.[15] It is composed of some small, undifferentiated cells, but mostly of large, highly differentiated, oval or polyhedral cells with a finely granular basophil cytoplasm and single or multiple nuclei. These cells have no counterpart in the pars anterior. They are arranged in trabeculae and in palisades about the blood vessels. They form perivascular spaces and larger follicles filled by a colloid that in origin is partly degenerative and partly secretory. This pars intermedia presents all extremes of variation. In one species it may be a prominent part of the gland and in another species insignificant. In different members of a given species it varies widely, and even in the same individual it changes from time to time (Rasmussen[14]).

12. Jaffé, R. H.: Histologic Studies on the Fat Content of the Normal Human Thyroid, Arch. Path. **3**:955, 1927.

13. Kraus, E. J.: Die Lipoidsubstanzen der menschlichen Hypophyse und ihre Beziehung zur Sekretion, Beitr. z. path. Anat. u. z. allg. Path. **54**:520, 1912.

14. Rasmussen, A. T.: Morphology of Pars Intermedia of the Human Hypophysis, Endocrinology **12**:129, 1928.

15. Thaon, P.: L'hypophyse, Paris, G. Doin, 1907.

In man, the pars intermedia, if present at all, is a rudimentary structure. Erdheim,[16] Berblinger,[17] Dayton,[18] Kasche, Benda and others insisted that man has no pars intermedia. Stendell,[19] Biedl,[20] Marburg,[21] Aschoff [22] and Schoenig [23] could not reconcile themselves to the view that in man the pars intermedia should be abruptly dropped. They have made a searching study for homologues in man of the pars intermedia of animals. One after another, various structures noted in the human hypophysis have been labelled in homology, "pars intermedia."

The zona intermedia, as seen in man, has nothing to do with a pars intermedia. Its cells are identical in origin, structure, function and variation with those of the rest of the anterior lobe. It is simply part of the pars anterior, which differs from the rest only in its greater content of colloid. Other structures have been even more readily confused. The posterior wall of Rathke's pouch, in man as well as in lower animals, is a multipotent layer. Besides differentiating into the cells of the pars intermedia, as it does to such an extent in lower animals, it can differentiate into a great variety of other structures. Its pharyngeal origin accounts for the appearance of ciliated and goblet cells, squamous cells and glandlike structures resembling mucous or salivary glands. Basophil cells and principal cells with colloid follicles like those of the anterior lobe are also formed from it, and undifferentiated fetal cells are found scattered among them. Whatever it differentiates, the posterior wall pushes into the adjacent pars nervosa in the same position that is occupied by the true pars intermedia. Basophil cells of the pars anterior proper, which have originated from the anterior wall of Rathke's pouch, also wander into the posterior lobe.

But all these do not constitute a pars intermedia, even if they lie in the same position. They have no resemblance to pars intermedia

16. Erdheim, J.: Pathologie der Hypophysen-Geschwülste, Ergebn. d. allg. Path. u. path. Anat. **21**:482, 1926.

17. Berblinger, W.: Kritisches zur Hypophysen-Pathologie, Frankfurt. Ztschr. f. Path. **35**:497, 1927.

18. Dayton, T. R.: Ueber die sogenannte Pars intermedia der menschlichen Hypophyse, Ztschr. f. Anat. u. Entwcklngsgesch. **81**:359, 1926.

19. Stendell, V.: Die Hypophysis cerebri, Lehrbuch der vergleichanden mikroskopischen Anatomie, Jena, Gustav Fischer, 1914.

20. Biedl, A.: Die funktionelle Bedeutung der einzelnen Hypophysenanteile, Endokrinologie **3**:241, 1929; Internal Secretory Organs, New York, William Wood & Company, 1913.

21. Marburg, O.: Zur Frage der Pars intermedia der menschlichen Hypophyse, Endokrinologie **5**:198, 1929.

22. Aschoff, L.: Gibt es eine Pars intermedia in der menschlichen Hypophyse? Beitr. z. path. Anat. u. z. allg. Path. **84**:273, 1930.

23. Schoenig, A.: Die extra-uterinen Entwicklungsphasen der Pars intermedia der menschlichen Hypophyse, Frankfurt. Ztschr. f. Path. **34**:482, 1926.

cells. They have the same structure as the pars anterior elements. They undergo the same changes as do the pars anterior cells in pregnancy, castration and many pathologic conditions. They are still to be identified with the pars anterior and not with the pars intermedia. The pars intermedia is simply one of the highly specialized differentiations which the posterior wall of Rathke's pouch can originate, and it has no homologue in these other structures described as occurring in man.

There are some indications, however, that man really has a pars intermedia, rudimentary and insignificant and functionless though it is. Maurer,[10] Lewis,[24] Lewis and Lee,[25] Marburg,[21] Loeffler [26] and others have described from time to time the occasional finding in the posterior lobe of groups of cells that resemble somewhat those of the pars intermedia. I found similar cells incidentally in a case a report of which I recently submitted for publication. It is almost impossible, however, to establish the identity of these small and infrequent cellular structures because of the poor fixation of most human material. In two cases in which autopsy was performed soon after death, Dr. Bensley showed me cells in the pars posterior of the hypophysis that greatly resembled those of the pars intermedia of lower animals. But no absolutely specific histologic identification of them has as yet been made.

As one argument against its presence in man, Berblinger [27] pointed out that no tumor of the pars intermedia had ever been definitely established. Ewing,[28] however, quoted reports on three cases by Boyce and Beadles and Cushing, in which the relations of the hypophyseal tumor suggested an origin from the pars intermedia. Lewis [24] offered another case. The tumors were composed of cords of large cells, lying in acinar arrangement about colloid-filled spaces. They thus resembled thyroid gland tissue somewhat as does the pars intermedia. Two of these tumors were attached to the pedicle of the hypophysis above the sella, apparently originating from the pars tuberalis. The other two were adenomatous tumors that originated outside the main substance of the pars anterior and compressed it. The resemblance of these tumors to

24. Lewis, Dean: A Contribution to the Subject of Tumors of the Hypophysis, J. A. M. A. **55**:1007, 1910.

25. Lewis, Dean; and Lee, F. C.: On the Glandular Elements in the Posterior Lobe of the Human Hypophysis, Bull. Johns Hopkins Hosp. **41**:241, 1927.

26. Loeffler, E.: Ueber ortsfremde Zellen und Geschwülste im Hinterlappen und im Stiel der Hypophyse, Virchows Arch. f. path. Anat. **274**:326, 1929.

27. Berblinger, W.: Die genitale Dystrophie in ihrer Beziehung zu Stoerungen der Hypophysenfunktion, Virchows Arch. f. path. Anat. **228**:151, 1920.

28. Ewing, J.: Neoplastic Diseases, Philadelphia, W. B. Saunders Company, 1928.

the pars intermedia of animals is rather vague and is based only on the presence of numerous colloid-filled cysts. Nor does their origin outside the main mass of the pars anterior establish them as tumors of the pars intermedia, for rests of pars anterior cells are scattered all along the stalk and may just as well have produced adenomas which by colloid degeneration came to resemble somewhat, pars intermedia tissue.

The colloid masses and follicles of the adenoma herein reported also resembled these tumors. The columns and palisades of large, undifferentiated cells conformed to none of the more usual adenomas of the anterior lobe. The main substance of the anterior lobe itself was seen to form a thin capsule around the tumor mass. It was suggested that here at last one was dealing with the much sought for tumor of the pars intermedia. But this, too, was no tumor of the pars intermedia. It was composed of undifferentiated fetal cells and not of differentiated pars intermedia cells. Its abundant colloid, like that of the intermediate zone of the normal hypophysis, was a degenerative product from the undifferentiated cells rather than a secretory one. The tumor did not compress the anterior lobe, but rather expanded the lobe into a thin shell, which completely encapsulated it. Apparently it had started in the midportion of the pars anterior, for the compressed anterior substance surrounded it on all sides, separating it from the sella, the operculum and the infundibulum. Even posteriorly, the compressed old zone intermedia, with its flattened cysts, separated it from the pars nervosa and denied it any possible origin from a pars intermedia. It was finally classified, therefore, as a fetal cell adenoma arising from the midportion of the pars anterior of the hypophysis.

The second case was that of a dermoid cyst of the hypophyseal area. Tissues adjacent to the hypophysis have a special predilection for inclusion tumors of all kinds. Many of these tumors present cysts and nodules filled by cholesteatomatous material that resembled mother-of-pearl, and so have been given the name of "Perlegeschwülste." In 1897, Bostroem [29] analyzed these tumors and pointed out that the intracranial cholesteatomatous cysts arise by embryonal inclusion of ectodermal cells, which are carried into the brain vesicles during the closure of the neural canal. Cysts with but few squamous epithelium cells and much cholesteatomatous material he classed as "simple cholesteatomas." If the squamous epithelial cell masses were more abundant, he called them "epidermoids," to emphasize their origin from epidermis. If other special structures of the skin were included, such as fetal hairs, sweat glands and sebaceous glands, he classed them as "dermoids," since

29. Bostroem, E.: Ueber piale Epidermoide, Dermoide und Lipome, und durale Dermoide, Centralbl. f. allg. Path. u. path. Anat. **8**:1, 1897.

they were derived from the whole dermis. These unigerminal tumors pass by the addition of mesodermal and endodermal elements gradually into the field of the bigerminal teratoid tumors and finally into the trigerminal true teratomas. One step further carries them to the fetal implantations or inclusios foetus in foetu, the double monsters.

Then Erdheim [16] traced a well defined group of tumors of this region to included remnants of the craniopharyngeal pouch. He found rests of pharyngeal epithelium in ten of thirteen cases which he examined carefully for them. They were all in the midline, but were scattered from the base of the brain all the way along the course of the hypophyseal duct to the nasopharynx. The inclusion tumors of the hypophyseal duct arise from these rests, at any point along its course. They appear in the hypophysis itself, as well as in tissue adjacent to it, but adhere to the midline.

They, too, in complexity of structure present a progressive series. There are simple cysts arising by distention of Rathke's pouch. They are sometimes lined in part by a ciliated epithelium, which indicates their origin from the nasopharynx and distinguishes them from ependymal, adenomatous or ectodermal inclusion cysts. The "epidermoid" tumors from the hypophyseal duct include intracystic papillomas, adamantinoid tumors and benign and malignant squamous cell tumors of all kinds. Often they are prone to hemorrhages and degenerative changes which lead to the metaplastic production of cartilage, bone and even bone-marrow. Hemosiderin deposited from the hemorrhages may be confused with melanin. Pseudoxanthomatous, fat-laden cells may be taken for notochord tissue. Glia cells of the adjacent brain tissue may be taken for part of the tumor, and so these degenerating hypophyseal duct tumors be mistaken for teratomas.

Erdheim sharply distinguished these tumors from the dermoid tumors of Bostroem. Hypophyseal duct tumors adhere to the midline, the dermoid tumors do not. He found keratohyaline granules in the latter, but not in the former. Subsequent study failed to confirm this distinction, because when fresh material was used, keratohyaline granules were found just as readily in tumors of the hypophyseal duct as in the others.[30] Fetal hair follicles and sebaceous glands, or endodermal elements, were still considered as irrefutable marks of dermoid origin, as opposed to hypophyseal duct origin. But, according to Ewing, it is even possible for true teratoid tumors to arise, autochthonously, by metaplasia from hypophyseal duct remnants. Practically all absolute

30. Horrax, G.: A Consideration of Dermal Versus Epidermal Cholesteatomas Having Their Attachment in Cerebral Envelopes, Arch. Neurol. & Psychiat. **8**:265, 1922.

distinction therefore vanishes, except that the latter tumors adhere to the midline. Both groups, indeed, are derivatives of embryonically included stratified squamous epithelium. Bostroem's tumors are derived from external ectoderm and Erdheim's tumors from oral ectoderm. The tumor of the second case was definitely of squamous epithelial character. The central cyst was filled by cholesteatomatous material. Its wall was lined by stratified squamous epithelium with intercellular bridges, keratohyaline granules and hornified epithelial pearls. There were calcium deposits and degenerative and reactive changes in the adjacent brain tissue. The cartilage and bone and vascular stroma of the cyst wall might be taken as metaplastic in origin, but the fetal hair follicles take it undeniably from the class of epidermoids to that of dermoids. The cells resembling embryonic fat cells are further evidence of this. These structures and the asymmetric position of the tumor place it with the dermoid cysts of external ectodermal inclusion, rather than with the hypophyseal duct tumors of oral ectodermal inclusion.

Since Erdheim's clarification of the subject, a considerable number of hypophyseal duct tumors have been described (Duffy,[31] Jackson,[32] Kanavel[33]). Of external ectoderm inclusion tumors many of the simple cholesteatomas and epidermoids, not containing hair, have also been described (Bailey,[34] Schuster[35]). Hair-containing cholesteatomas, or true dermoid cysts, are less numerous (Teutschländer,[36] Rand,[37] Tannenhain,[38] Koprewa[39]). Globus[40] described a case almost identical with the one here reported, except that sebaceous gland cells were present. He distinguished these from embryonic fat cells because their nuclei were pyknotic and their cytoplasmic vacuoles irregular.

31. Duffy, W. C.: Hypophyseal Duct Tumors, Ann. Surg. **72**:537, 1920.

32. Jackson, H.: Craniopharyngeal Duct Tumors, J. A. M. A. **66**:1082, 1916.

33. Kanavel, A. B., and Jackson, H.: Cysts of the Hypophysis, Surg. Gynec. Obst. **26**:61, 1918.

34. Bailey, P.: Cruveilheir's "Tumeurs Perlées," Surg. Gynec. Obst. **31**:390, 1920.

35. Schuster, J.: Dermoid Cyst of Right Frontal Lobe, Schweiz. Arch. f. Neurol. u. Psychiat. **16**:327, 1925.

36. Teutschländer, O. R.: Zwei seltenere tumorartige Bildungen der Gehirnbasis, Virchows Arch. f. path. Anat. **218**:224, 1914.

37. Rand, C. W.: Intracranial Dermoid Cyst, Arch. Neurol. & Psychiat. **14**: 346, 1925.

38. Tannenhain, C.: Dermoid Cyste des dritten Gehirnventrikels, Wien. klin. Wchnschr. **10**:494, 1897.

39. Koprewa, G.: Eine Dermoidcyste in der linken Grosshirnhemisphaere, Med. Klin. **23**:645, 1927.

40. Globus, J. H.: Teratoid Cyst of the Hypophysis, Arch. Neurol. & Psychiat. **9**:417, 1923.

More complex, bigerminal teratoid tumors are infrequent (Derman [41]). Gautier [42] collected from the literature only twenty-five cases described with sufficient histologic accuracy to warrant their classification with teratoid tumors. True trigerminal teratomas are rare indeed. Sztanojevits [43] described one case and Saxer [44] another. Kraus [45] recently completed the series by reporting an epignathous monster of the hypophyseal region.

Tumors of the hypophysis and tissues adjacent to it have attracted particular attention because of the special syndromes with which they are associated. The hypophysis itself has several distinct endocrine functions which may be either stimulated or destroyed. The hypophyseal region about it is an apex of vegetative control. When one attempts to analyze the syndromes produced by these tumors, one wanders into uncertain territory. Hypophyseal tumors may be eliciting symptoms by secondary pressure on the midbrain. Tumors of the midbrain may manifest themselves only through destruction or dysfunction of the hypophysis.[46]

Tumors that involve one part while leaving the other perfectly free are, however, equivalent in man to experimental selective extirpation in animals. They contribute to the evidence by which one may some day be able properly to assign the various functions of this region. Such cases have already taught that many of the functions that formerly were regarded as belonging to the hypophysis are really functions of the midbrain (Illig [47]).

For a long time, the posterior lobe of the hypophysis was implicated in the cause of diabetes insipidus, because lesions of the hypophysis were often associated with this syndrome. In the early experiments on

41. Derman, G. L.: Zur Kenntnis der Teratome des Gehirns, Virchows Arch. f. path. Anat. **259**:767, 1926.

42. Gautier, R.: Zur Kenntnis der Mischgeschwülste der Hypophysengegend, Frankfurt. Ztschr. f. Path. **19**:247, 1916.

43. Sztanojevits, L.: Mannfaustgrosses, lange Zeit hindurch ohne objective Symptome bestehendes und ploetzlich zum Tode fuehrendes Klein-Hirnteratom, Neurol. Centralbl. **37**:784, 1918.

44. Saxer, F.: Ein zum groessten Theil aus Derivaten der Medullarplatte bestehendes grosses Teratom im dritten Ventrikel eines sieben woechentlicher Kindes, Beitr. f. path. Anat. u. z. allg. Path. **20**:399, 1897.

45. Kraus, E. J.: Ueber ein epignathisches Teratom des Hypophysengegend, Virchows Arch. f. path. Anat. **271**:546, 1929.

46. Lereboullet, P.; Mouzon, J., and Catholu, J.: Infantilisme dit hypophysaire par tumeur du troisième ventricule, integrite de l'hypophyse, Rev. neurol. **28**:154, 1921.

47. Illig, W.: Geschwülste der Hypophyse beziehungsweise der Hypophysengegend und Zwischenhirn, Virchows Arch. f. path. Anat. **270**:549, 1928.

animals, destruction of the pars posterior resulted in polyuria, which injections of extracts from the posterior lobe relieved. However, it was then observed that pathologic processes involving practically the whole hypophysis were not necessarily followed by diabetes insipidus. Traumatic, infectious and neoplastic processes of all kinds affecting the region of the tuber cinereum and leaving the hypophysis anatomically intact could alone produce diabetes insipidus (Leschke,[48] Bosco [49]).

In reevaluating the results of hypophysectomy it was noted that polyuria did not occur in every case. When polyuria occurred following hypophysectomy, pathologic changes, such as necrosis, cysts, hemorrhages, tigrolysis, etc., were always found also in the tuber cinereum. When polyuria did not occur, these changes were absent (Karlik [50]).

On repetition of the experiments, extirpation of as much of the hypophysis as possible (fully 95 per cent or more) did not lead to polyuria if the base of the brain was avoided (Bailey and Bremer,[51] Fulton and Bailey [52]). Superficial lesions of the tuber cinereum produced polyuria even when the hypophysis was intact.

Clearly this indicated that diabetes insipidus is not a symptom of depletion (an "Ausfallerscheinung") of the pars posterior, but is a result of specific damage to the tuber cinereum at the base of the brain. The two cases herein reported, despite the brief clinical observation of them, lend some support to this view. In the first, the fetal cell adenoma had crushed the original hypophysis into a thin shell around it; yet there was apparently no polyuria. In the second, the clinical picture was complicated by the paretic changes, but the dermoid cyst had produced extensive damage in the hypothalamus and had affected the hypophysis but little, and there was polyuria. In Globus's case, too, there was diabetes insipidus with the hyophysis intact.

The hypophysis has been given a rôle also in sugar metabolism. Glycosuria and diabetes are often associated with acromegalic tumors. Injury to the hypophysis causes a transient hyperglycemia. In the case of the dermoid cyst here reported, the hypophysis was intact, yet there were hyperglycemia and glycosuria which yielded promptly to insulin and caused confusion with diabetes mellitus. In fact, the same hyper-

48. Leschke, E.: Beitraege zur klinischen Pathologie des Zwischenhirns, Ztschr. f. klin. Med. **87**:201, 1919.

49. Bosco, G.: La patogenia de la diabetes insipida, Semana méd. **2**:477, 1925.

50. Karlik, L. N.: Zur Frage der sogenannten hypophysaeren Polyurie, Ztschr. f. d. ges. exper. Med. **61**:5, 1928.

51. Bailey, P., and Bremer, F.: Experimental Diabetes Insipidus, Arch. Int. Med. **28**:773, 1921.

52. Fulton, J. F., and Bailey, P.: Brain Tumor in Region of Third Ventricle, J. Nerv. & Ment. Dis. **69**:1, 145 and 261, 1929.

glycemia and glycosuria seen with tumors of the hypophysis may be seen with tumors of the hypothalamus that do not involve the hypophysis.[53] Injury of the tuber cinereum gives an even greater hyperglycemia than does that of the hypophysis. Therefore, a "sugar center" has been postulated in the tuber cinereum, rather than in the pituitary body.

There is no definite "sugar center" in the hypophysis. Neither is there one in the tuber cinereum or in any other part of the brain. Tumors in other parts of the brain may occasionally cause glycosuria. Injury of any part of the brain can cause hyperglycemia and glycosuria (Hiller[54]). While the hypothalamic diabetes cannot be ascribed to any definite "sugar center" in this region, it is known that the diencephalon has a certain regulatory influence on various vegetative functions, including the metabolism of fat, salt, water and sugar, and sleep (Fulton and Bailey[52]). It is damage to this region that is chiefly responsible for the adiposity, the diabetes mellitus and the diabetes insipidus formerly ascribed to hypephyseal lesions.

SUMMARY AND CONCLUSIONS

A fetal cell adenoma of the hypophysis and a dermoid cyst of the hypothalamus are reported. The first tumor resembled one of the so-called "pars intermedia tumors." It originated, however, not from a pars intermedia, but from the midportion of the pars anterior. It was composed not of the specific differentiated pars intermedia cells, but of undifferentiated fetal cells. If man has a pars intermedia comparable with that of lower animals, it is rudimentary, variable and functionless. There is, as yet, no histologic proof establishing its presence.

The dermoid cyst belonged to the group of inclusion tumors of the hypophyseal area. It was derived from embryonal rests of cranial external ectoderm included during the invagination of the brain vesicles. It was related to Erdheim's tumors derived from rests of oral ectoderm invaginated with Rathke's hypophyseal pouch. It involved the hypothalamus, leaving the hypophysis relatively intact, and yet produced the diabetes insipidus and the diabetes mellitus usually ascribed to hypophyseal lesions. The diencephalon rather than the hypophysis is chiefly responsible for these syndromes.

53. Klug, W.: Die Hypophyse und der Zuckeraushalt des Koerpers, Deutsche Ztschr. f. Chir. **212**:5, 1928.

54. Hiller, F., and Grinker, R.: The Nervous Regulation of Sugar Metabolism, Arch. Neurol. & Psychiat. **22**:919, 1929. Hiller, F., and Tannenbaum, A.: The Nervous Regulation of Sugar Metabolism, Arch. Neurol. & Psychiat. **22**:901, 1929.

SYPHILITIC CORONARY ARTERITIS *

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Stenosis or obliteration of the ostia of the coronary arteries is generally recognized to be a common complication of syphilitic aortitis. In most of the standard textbooks and reference books of pathology, mention is made of frequent occurrence of this complication, and several authors have emphasized its clinical importance. Scott [1] recently stressed the significance of the coronary involvement in the relative incapacity of the heart for compensation in cases of syphilitic aortic insufficiency. MacKenzie [2] regarded coronary stenosis as one of the most common causes of sudden death from cardiac failure in syphilitic aortitis.

It is of interest that the various investigators of syphilitic vascular disease have almost without exception regarded the coronary involvement as being limited to that part of the coronary artery included in the wall of the aorta and the stenosis as being due to aortic rather than to coronary disease. The opinions expressed by Benda,[3] MacCallum [4] and Jores [5] are that the coronary circulation is impaired by the periosteal intimal proliferation in the aorta, and that syphilis of the coronaries, per se, is rare or nonexistent.

Kaufmann [6] stated that endarteritis of the coronaries occurs in the course of syphilitic aortitis and leads in some instances to total closure of the ostia of the vessels. Warthin [7] also observed the occurrence of syphilitic thrombo-arteritis obliterans of the coronaries, but expressed the opinion that it is not of frequent occurrence. In three studies of

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1. Scott, R. W.: Syphilitic Aortic Insufficiency, Arch. Int. Med. **34**:645, 1924.

2. MacKenzie, I.: Syphilis of the Circulatory System, Glasgow M. J. **92**:209, 1919.

3. Benda, C.: Die Gefaesse, in Aschoff, Ludwig: Pathologische Anatomie, Jena, Gustav Fischer, 1923, vol. 2, p. 73.

4. MacCallum, W. G.: A Text-Book of Pathology, Philadelphia, W. B. Saunders Company, 1925, p. 351.

5. Jores, L.: Herz und Gefaesse, in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1924, vol. 2, p. 668.

6. Kaufmann, E.: Lehrbuch der speziellen pathologischen Anatomie, Berlin, W. de Gruyter & Company, 1922, vol. 1, p. 43.

7. Warthin, A. S.: Syphilis of the Medium and Smaller Arteries, New York M. J. **115**:69, 1922.

syphilis of the medium-sized vessels (Herxheimer,[8] Turnbull,[9] Saphir [10]), the coronary arteries are not considered as being the seat of syphilitic arteritis. Each of these investigators notes the frequent occurrence of stenosis or occlusion of the coronary orifices in syphilitic arteritis, but considers the change to be due to the disease in the wall of the aorta. In regard to aortic insufficiency, Scott stated: "In this connection it is interesting to note that in spite of the active disease surrounding the orifices, the coronary vessels themselves were seldom involved. When opened, they presented a smooth, normal intima."

A lesion of such vital clinical interest deserves thorough pathologic examination. Statistical studies have indicated that syphilitic aortitis occurs in 7 per cent of all cases coming to autopsy (Oberndorfer [11]), and that in cases of syphilis the percentage of aortic involvement reaches 82 (Stadler [12]).

This study is not intended to represent a statistical investigation. Eight cases in which there was syphilitic aortitis with stenosis or obliteration of one or of both coronary arteries were selected for study. Representative blocks from various portions of the coronary arteries, myocardium, aortic valve and aorta were taken for histologic examination. Sections were stained with hematoxylin and eosin and by van Gieson's picrofuchsin, Saphir's orcein-hematoxylin and Warthin-Starry's silver methods. The silver stains for spirochetes were controlled by sections of congenitally syphilitic liver in which spirochetes were readily identified.

REPORT OF CASES

CASE 1.—W. M., a white man, aged 65, entered the hospital complaining of shortness of breath, nausea, vomiting and dependent edema. To within a few days before admission, the patient had been in good enough health to climb three flights of stairs to his room each day without assistance. There had been no previous symptoms of cardiac failure and no history of anginal attacks. The Wassermann reaction of the blood was ++++.

His course in the hospital was one of progressive decline. There was no response to digitalis. He died on the ninth day of hospitalization. The clinical diagnosis was congestive heart failure and syphilitic aortitis with aortic insufficiency.

The pathologic diagnosis was: chronic syphilitic aortitis; chronic syphilitic aortic valvulitis with insufficiency; chronic obliterative arteritis of the proximal portions and orifices of the coronary arteries, cardiac hypertrophy and dilatation;

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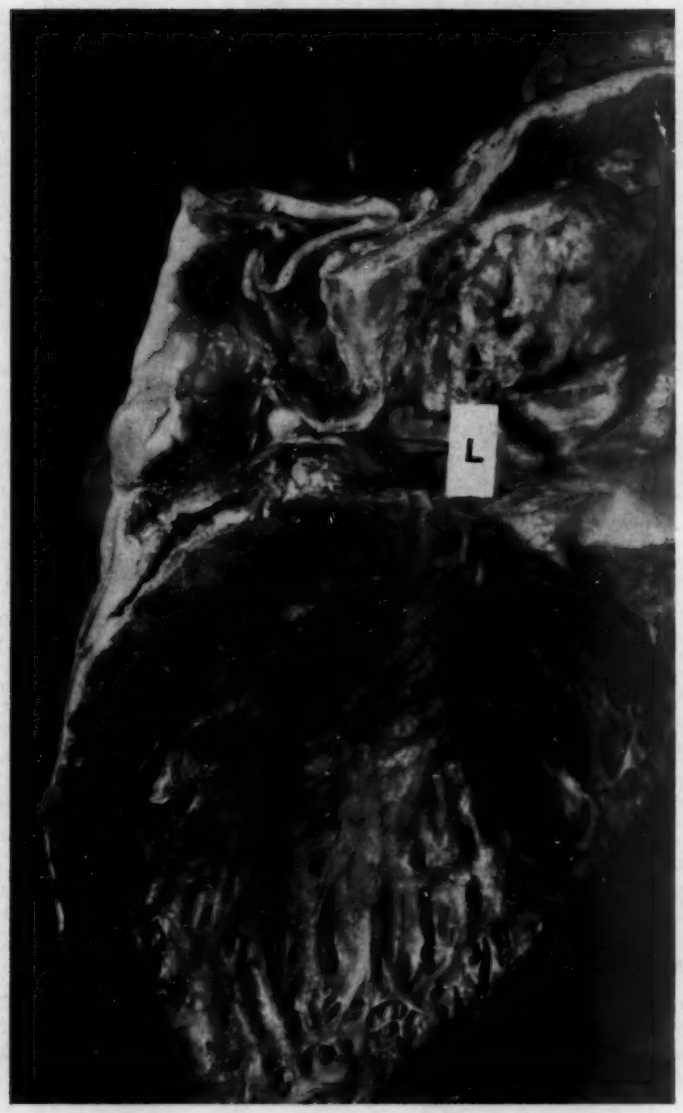

Fig. 1 (case 1).—Stenosis of the proximal portion of the left coronary artery by chronic obliterative arteritis (three-fourths actual size).

chronic interstitial myocarditis, fatty degeneration of the myocardium, mural thrombosis of the right and left auricles; passive hyperemia of the lungs, liver, kidneys and spleen, and recent infarcts of the lungs.

The heart weighed 590 Gm. (fig. 1). The hypertrophy was preponderantly of the left ventricle, with dilatation of all chambers. The myocardium was soft, flabby and pale grayish brown. The aortic valve was incompetent, with thicken-

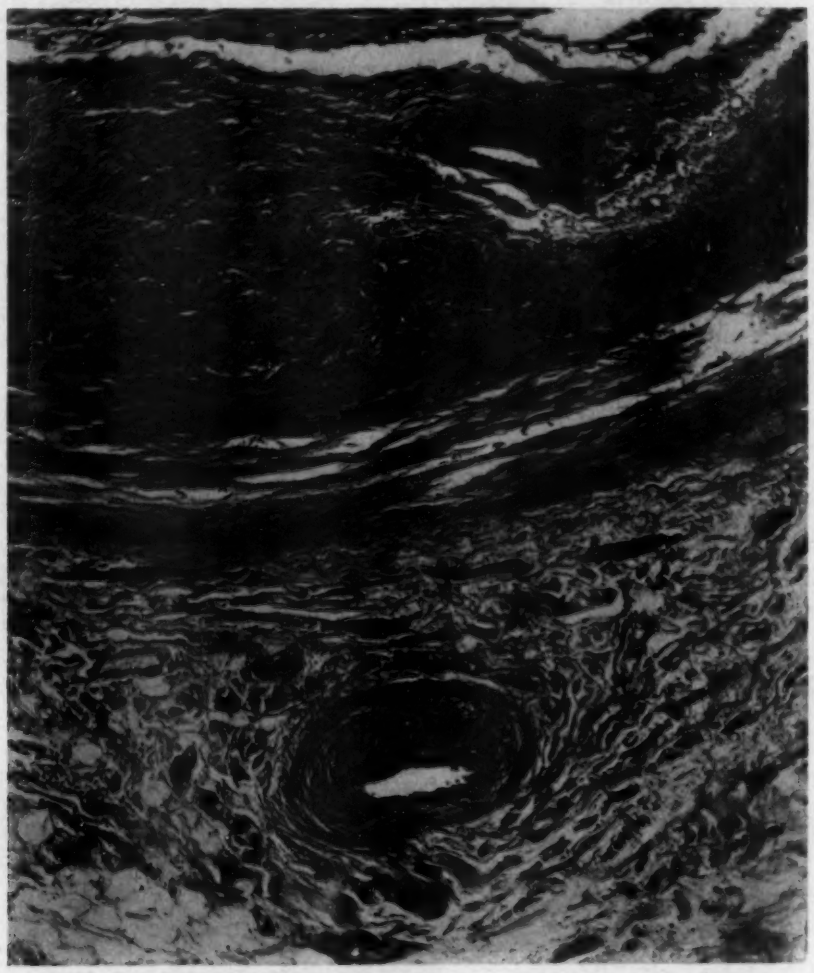

Fig. 2 (case 1).—Obliterating endarteritis of vasa in the wall of the right coronary; × 160.

ing and shortening of the cusps and separation of the commissures. The aortic ring measured 9 cm. in circumference.

The aorta was thin-walled and dilated. There was marked intimal sclerosis with formation of translucent, grayish-blue plaques and pitting and longitudinal wrinkling of the intima. There were many interruptions in the continuity of the media by fibrous scars, with irregularity in its thickness. The disease extended through the entire thoracic and most of the abdominal aorta.

The ostium of the right coronary artery was completely obliterated, and over its site was a thick, calcified, atheromatous plaque. For a distance of 1 cm. from the aorta, the right coronary artery was represented by a solid fibrous cord; when this was sectioned transversely, the media appeared greatly thickened, and the lumen of the artery was occluded by what appeared to be intimal proliferation.

Histologic examination of sections through the first centimeter of the right coronary showed fairly well preserved media and dense fibrous adventitia, which

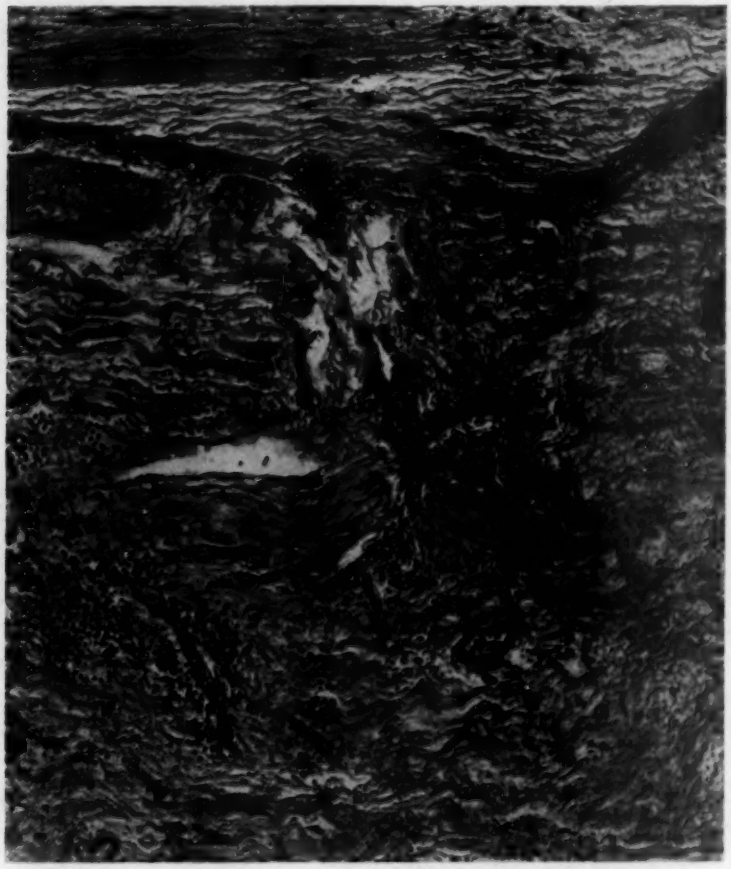

Fig. 3 (case 1).—A vascularized, fibrous scar extending from the adventitia into the peripheral portion of the media of the left coronary; × 130.

was continuous with a wide zone of perivascular fibrosis. In the adventitia were a large number of vasa many of which were partially or completely obliterated by endarteritis (fig. 2). There were many foci of lymphocytes and plasma cells, often of perivascular distribution. Occasional fan-shaped vascular scars extended into the media, with resulting disruption of elastic lamellae. The lumen of the vessel was completely obliterated by dense and, in places, calcified, fibrous connective tissue, in which occasional phagocytes containing blood pigment indicated that thrombosis had occurred.

The proximal 8 mm. of the left coronary artery was stenosed, but not completely obliterated (fig. 1). Its lumen over a distance of about 5 mm. admitted the passage of a 1 mm. probe with considerable resistance, and it did not seem likely that there was any considerable functional patency. The same microscopic changes (fig. 3) were seen here as were described for the right coronary, except that there was less intimal proliferation and an absence of the complete obliteration of the lumen.

Except for a mild degree of intimal sclerosis in the ramus descendans of the left coronary, there were no other pathologic changes in the coronary system. No accessory or aberrant arteries could be demonstrated. The stomas of several large thebesian vessels in the left ventricle were identified macroscopically. An

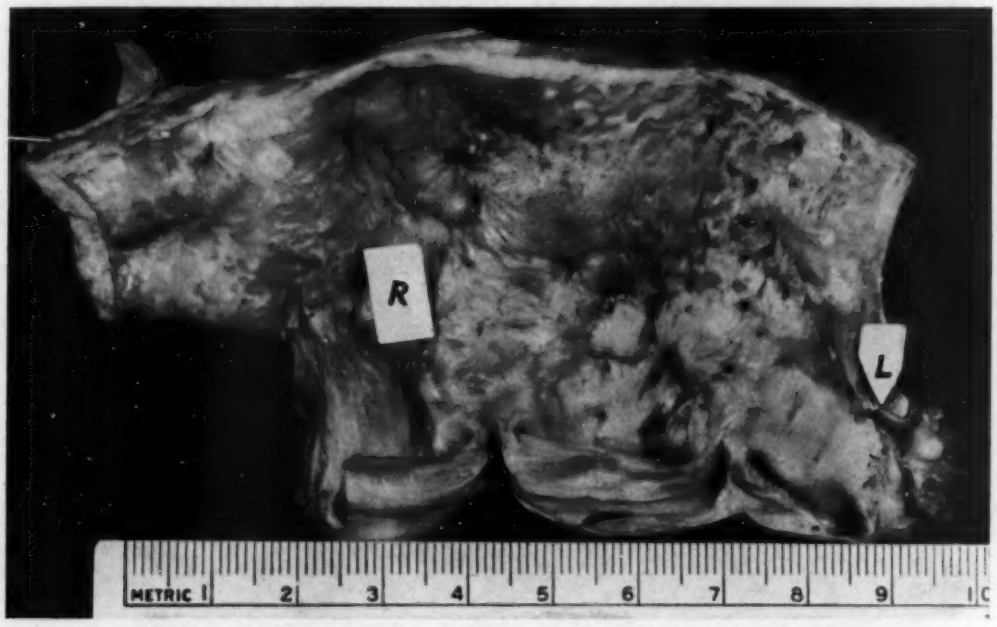

Fig. 4 (case 2).—Proximal portion of the aorta, including the aortic valve. The right coronary is obliterated just distal to the aorta, the ostium being patent. The aortic portion of the left coronary is stenosed (actual size).

attempt was made by means of serial sections to demonstrate communication between the thebesian and the coronary circulation, but the series was inconclusive.

The myocardium was the seat of diffuse interstitial fibrosis, and throughout there were many small stellate scars not associated with exudation. In many areas, the fibrosis was perivascular and was the seat of myxomatous change. There was marked, generalized fatty degeneration of muscle cells.

Stains for spirochetes on sections of aorta, coronary arteries and myocardium were negative.

CASE 2.—J. B., a white man, 44 years of age, was unconscious when admitted to the hospital. Just before admission, the patient had been seized with a sudden severe epigastric pain and loss of consciousness. There was no history of cardiac decompensation, but friends stated that the patient had complained of a similar

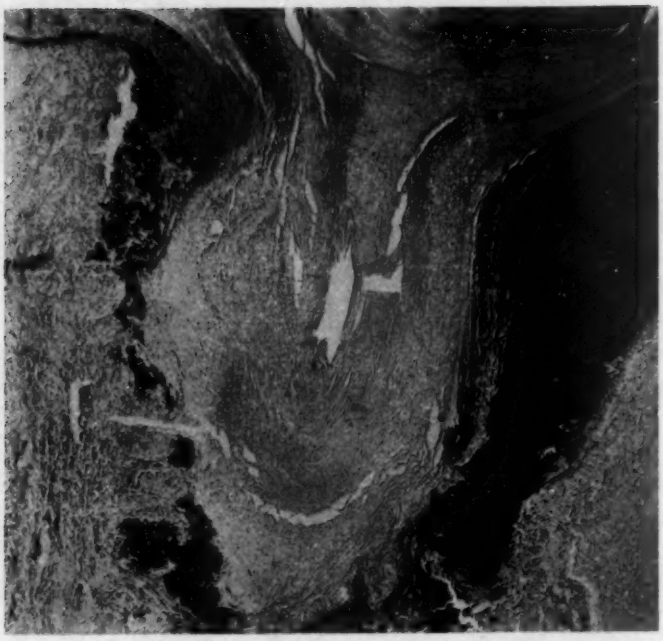

Fig. 5 (case 2).—A tangential section through an obliterated segment of the right coronary artery distal to the aorta; elastic stain; × 12.

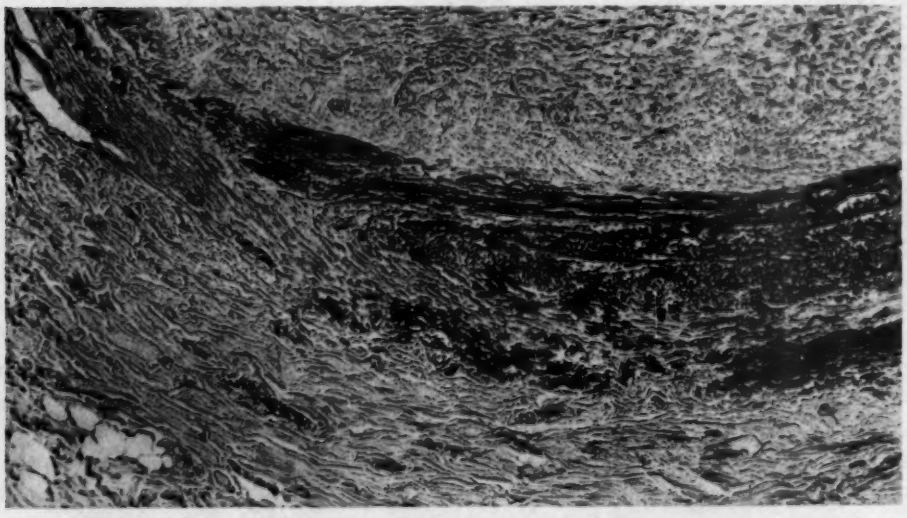

Fig. 6 (case 2).—A section through the wall of the right coronary showing disruption of the elastica and intimal proliferation; elastic stain; × 110.

attack of epigastric pain and loss of consciousness a few week before. The patient died without rallying from the circulatory collapse. The clinical diagnosis was: coronary thrombosis. No blood was taken for the Wassermann test.

The pathologic diagnosis was: active syphilitic aortitis, active syphilitic aortic valvulitis, chronic obliterative syphilitic arteritis of the proximal portion of the right coronary artery, stenosis of the orifice of the left coronary artery, cardiac hypertrophy and dilatation, subacute fibrinous pericarditis, emphysema, pulmonary edema, healed gastric ulcer and healed pulmonary tuberculosis.

The heart was enlarged to 480 Gm., the hypertrophy being principally of the left ventricle. There was moderate dilatation of all chambers. The circumference of the aortic ring was 9 cm. and of the ascending arch 9.4 cm. The wall of the aorta was greatly thickened, measuring 5 mm. just above the aortic valve. Histologically there was a diffuse exudative, proliferative and degenerative inflammatory process involving the adventitia, media and intima, with formation of miliary gummas and large areas of granulation tissue. The change was typical of active syphilitic inflammation, with marked destruction of the wall of the aorta.

The leaflets of the aortic valve were only slightly shortened and thickened, with little commissural separation, and represented only a mild degree of insufficiency.

Both coronary ostia could be identified (fig. 4). The right was a small saccular outpouching of the aortic wall, and just distal to the dilated orifice the artery was completely stenosed over a distance of about 6 mm.

Histologically (fig. 5) there was a still intact endothelium-lined lumen, although it was not considered to be functionally patent. There were obliterating endarteritis of the vasa, perivascular infiltration of lymphocytes and plasma cells, with scarring of the media, and proliferation of the intima. The entire process was less active and presented more of the characteristics of chronicity than did the aortitis.

The orifice of the left coronary artery was reduced to a diameter of less than 1 mm., but the reduction continued only in that part of the artery which was included in the wall of the aorta. Distal to the aortic adventitia, the vessels showed no pathologic change. On microscopic examination, the coronary stenosis was found to be due to the surrounding productive inflammation in the aorta and not to disease of the coronary artery itself.

The myocardium, including branches of the coronary, showed no pathologic change other than some swelling and granularity of the muscle cells, with slight interstitial fibrosis.

Stains for spirochetes in the aorta were negative.

CASE 3.—N. H., a Negress, aged 24, entered the hospital with a complaint of precordial pain, vomiting and weakness. Ten days before admission, she had a sudden sharp substernal pain, which was followed by vomiting. Otherwise the history was essentially negative. The only significant clinical observations were increased palpable cardiac activity with persistent systolic and diastolic murmurs. The pulse rate varied from 55 to 105, and the blood pressure averaged 122 systolic and 60 diastolic. She died suddenly during the night of her sixth day in the hospital. The clinical diagnosis was: coronary or cerebral embolism. No Wassermann test was done.

The pathologic diagnosis was: active syphilitic arteritis involving the thoracic aorta, both coronaries, the innominate, the left common carotid, the left sub-

clavian and the superior mesenteric arteries, and obliteration of the right, and stenosis of the left, coronary orifices.

The heart weighed 280 Gm. and presented no gross evidence of pathologic change. The aortic ring measured 7.5 cm. in circumference, and the aortic valve appeared normal. The aorta beginning just above the ring and extending down to the diaphragm was greatly thickened, the wall measuring about 1.5 cm. in thickness through the arch. The lumen of the aorta was reduced. The intima was smooth, but had a diffuse grayish-blue, translucent appearance.

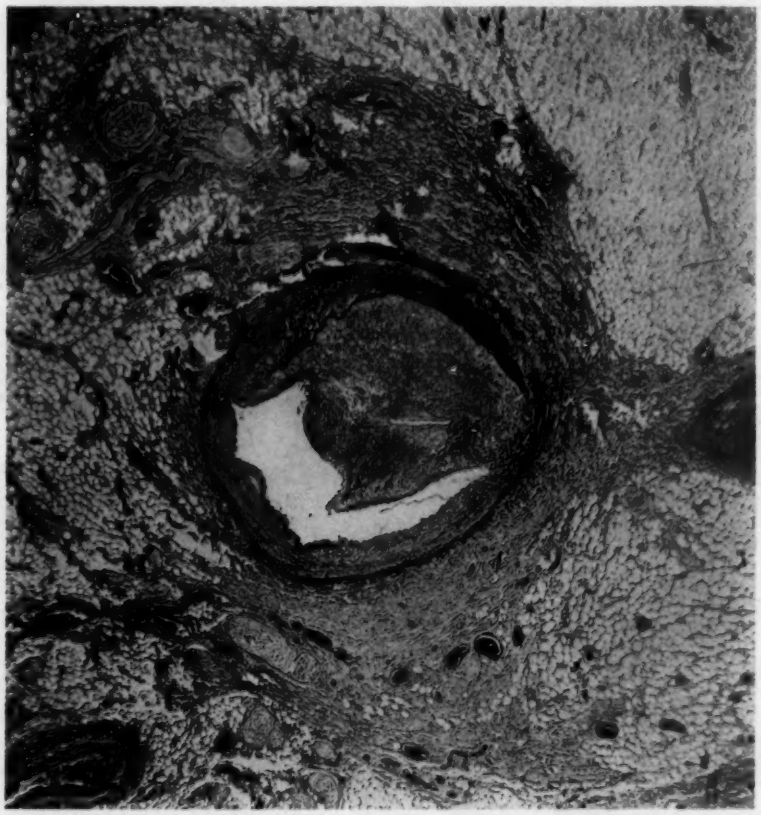

Fig. 7 (case 3).—The proximal portion of the right coronary artery. The lumen is partially occluded by vascularized granulation tissue, which is continous with fibrous proliferation in the media. Fragmentation of the elastica and proliferation of the adventitia are seen; elastic stain; × 18.

Histologic examination of the aorta showed the intima to measure from 2 to 3 mm. in thickness and to be, together with the superficial portion of the media, the seat of myxomatous degeneration. The media and adventitia were occupied by multiple foci of granulation tissue associated with the formation of new blood vessels, exudation of lymphocytic and endothelial cells, edema and small areas of coagulation necrosis with occasional giant cells. There was a marked obliterative endarteritis of the vasa.

The right coronary artery was completely obliterated for a distance of about 1 cm. by what appeared grossly to be intimal proliferation.

Histologic examination of sections through the obliterated segment of the right coronary artery (fig. 7) showed the lumen to be occluded by intimal proliferation.

Fig. 8 (case 3).—Elastic stain showing encroachment of the media of the left coronary by vascularized, fibrous connective tissue; × 300.

The proliferated intima was vascularized and the seat of lymphocytic infiltration. The media was traversed by radially disposed, vascularized, fibrous scars often extending into the intima. There was marked disruption of the continuity of the elastica (fig. 8). The vasa were the seat of an obliterative endarteritis, and in the adventitia and the wide surrounding zone of perivascular fibrosis there was marked exudation of lymphocytes and endothelial cells.

The left coronary artery admitted the passage of a small probe, but the patency of the lumen did not exceed a diameter of 1 mm. This reduction of patency extended for a distance of about 9 mm. from the orifice. On microscopic examination there was found to be a gumma with a diameter of approximately 5 mm. situated in the wall of the aorta immediately adjacent to the coronary

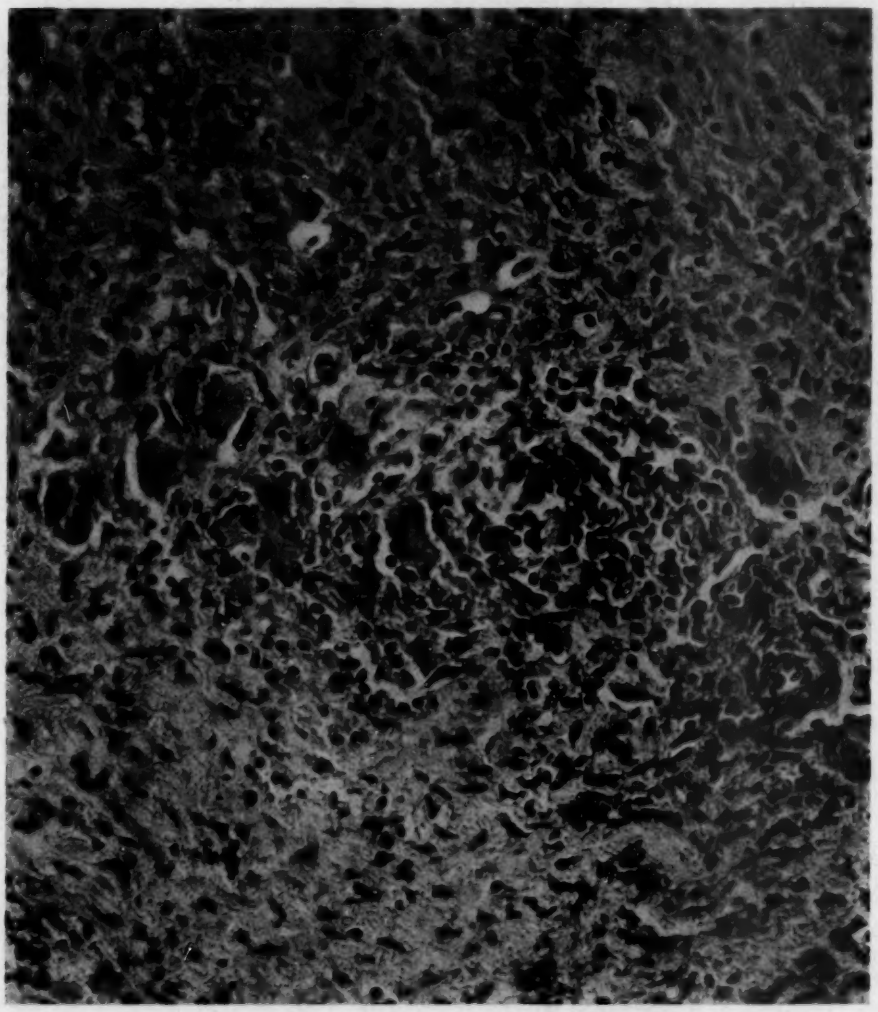

Fig. 9 (case 3).—Peripheral exudative zone of a gumma that impinged on the left coronary ostium; × 500.

orifice (fig. 9). This gumma had encroached on and compressed the coronary in its aortic portion. Distal to the aorta, extending as far as the stenosis, changes similar to those described for the right coronary, but without complete obliteration of the lumen, were present.

CASE 4.—A. H., a Negro, aged 55, was a cardiac invalid the last five years of his life. He had persistent hypertension, averaging 210 systolic and 130 diastolic. In five of his six periods of hospitalization, he was admitted with cardiac decompensation. Each time his heart was readily compensated on rest in bed and the administration of digitalis. There was no evidence of valvular heart disease or of aortitis, and the Wassermann reaction was negative. On the eighth day of the sixth hospitalization, the patient died suddenly from circulatory collapse. The clinical diagnosis was: coronary thrombosis.

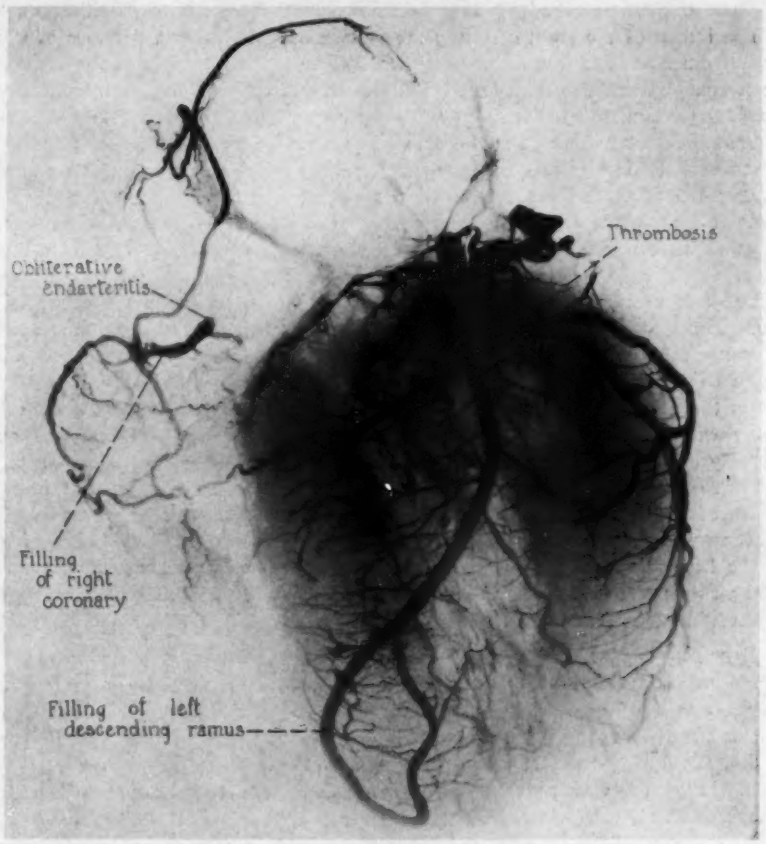

Fig. 10 (case 4).—Roentgenogram of the heart injected through the left coronary orifice. There is complete obliteration of the proximal portion of the right coronary artery and thrombosis of the descending ramus of the left.

The pathologic diagnosis was: thrombosis of the ramus descendans of the left coronary artery; chronic obliterative syphilitic arteritis of the proximal portion of the right coronary artery; cardiac hypertrophy and dilatation; chronic syphilitic aortitis; generalized, severe arteriosclerosis; mild arterionephrosclerosis, and generalized miliary tuberculosis.

Although active miliary tubercles were widely disseminated, their number was sparse, and they constituted an incidental microscopic observation.

The heart weighed 870 Gm., the hypertrophy being preponderantly of the left ventricle. There was little evidence of dilatation. The endocardium and the valves appeared normal. The aortic ring measured 8.8 cm. The leaflets were wide, deep and not thickened; there was no separation of the commissures. In the aorta there were two small saccular dilatations just above the aortic ring. There was pronounced intimal sclerosis throughout the entire aorta, with pitting, longitudinal scarring, formation of hyaline plaques and calcification. Histologically, the changes in the aorta were of a chronic nature, with obliterating arteritis of the vasa and medial scarring and degeneration, without prominent vascularization and with but little exudation. There was marked intimal sclerosis with calcification.

The lumen of the right coronary artery was occluded over a distance of about 1 cm. from its orifice, the latter being marked by a small dimple in the intima of the aorta. There was no reduction in the diameter of the vessel, even in its occluded portion, the obliteration being by fibrous proliferation into the lumen. Microscopic examination of the obliterated segment of the right coronary indicated a pathologic change of long duration, with partial calcification of the dense fibrous cicatrix that occupied the lumen of the vessel. The continuity of the elastic fibers of the media was interrupted by many small, dense, fan-shaped, fibrous scars radiating in from the adventitia. There were extensive hyalinization of the media and some perivascular lymphocytic infiltration of the media and adventitia.

The left coronary orifice was greatly distended, as was also the proximal 15 mm. The entire left coronary appeared unusually large, but there was neither gross nor microscopic evidence of syphilis of any portion. The major descending ramus of the left coronary was anomalous in its course and extended obliquely across the anterior surface of the left ventricle. The proximal segment of this artery was occluded by an organized thrombus, which was superimposed on a partially obstructive ulcerated atheromatous plaque. A 17 per cent suspension of bismuth oxychloride in water containing 10 per cent acacia was injected into the orifice of the left coronary artery at a pressure of 120 mm. of mercury. The injection was continued over a period of four hours and was preceded by perfusion of the heart through the left coronary with saline solution until the perfusing fluid was free from blood. After injection the vessel was tied, and roentgenograms were taken (fig. 10).

Case 5.—J. J., a Negress, aged 48, died during her first period of cardiac decompensation. Symptoms of heart failure became progressively more severe over a period of months, and her death followed a sudden circulatory collapse that occurred two weeks after admission. There was no response to strophanthin or digitalis during the last period of hospitalization. The clinical diagnosis was: syphilitic aortitis with aortic valvular insufficiency and chronic myocarditis. The Wassermann reaction of the blood was ++++.

The pathologic diagnosis was: chronic syphilitic aortitis, aneurysm of the abdominal aorta, chronic syphilitic aortic valvulitis with insufficiency, chronic syphilitic arteritis of the proximal portions of the coronary arteries, cardiac hypertrophy and dilatation, chronic interstitial myocarditis, generalized arteriosclerosis and chronic passive congestion of the lungs, liver and spleen.

The heart weighed 520 Gm. Both chambers were dilated, and the myocardium was pale and tough. The aortic valve ring measured 10 cm. in circumference and was obviously incompetent. The commissures of the aortic valve were widened, leaving spaces 2 to 3 mm. wide between the valve cusps. The left coronary cusp was shortened, thickened and rolled in.

There was a fusiform dilatation of the ascending arch of the aorta, which reached a maximum circumference of 13 cm. The wall was thin and the intima

sclerosed and calcified. Longitudinal wrinkling, pitting and vascularization of the intima were present, and there were elevated, translucent collars surrounding the stomas of the intercostal arteries.

Both coronary orifices were stenosed, the stenosis being most marked in the wall of the aorta. The walls of the proximal portions of both coronaries were thickened for a few millimeters distal to the aorta. The left coronary orifice measured 1.5 mm., and the right 2 mm., in diameter. The rest of the coronary arterial system appeared normal, save for a mild degree of intimal sclerosis.

Sections of both coronaries taken about 5 mm. from their ostia showed little intimal proliferation and no degeneration or calcification of either media or intima. There was a considerable increase in adventitial fibrous connective tissue, and the vasa were the seat of marked intimal sclerosis, many of them being surrounded by lymphocytic infiltration. Occasional small vascularized radial scars extended into the media, with disruption of the elastica. Sections taken longitudinally through the orifice of the left coronary presented the same histologic changes with the addition of intimal proliferation and myxomatous degeneration of the media.

Case 6.—J. S., a Negro, aged 47, died during his second period of hospitalization for cardiac decompensation. There had been symptoms of cardiac failure over a period of nine months preceding his death. Electrocardiographic studies were not significant. The Wassermann reaction of the blood was ++++. Death was due to congestive heart failure, and a clinical diagnosis of syphilitic aortitis with aortic valvular insufficiency was made.

The pathologic diagnosis was: active syphilitic aortitis; aneurysm of the abdominal aorta, with erosion of the tenth, eleventh and twelfth thoracic and first lumbar vertebrae; chronic syphilitic arteritis of the proximal portion of the right coronary artery; cardiac hypertrophy and dilatation; fatty degeneration of the myocardium, and mild arteriosclerosis.

The heart weighed 680 Gm., the hypertrophy being participated in by both ventricles, with moderate dilatation. The myocardium was soft and mottled with yellow. The aortic valve ring measured 8.5 cm. in circumference, and the valve leaflets were slightly thickened, with a suggestion of separation of the commissures. The wall of the aorta was generally thickened, measuring 4 mm. just above the aortic ring. There were a fusiform dilatation of the arch, reaching a circumference of 9.75 cm., and a saccular aneurysm on the posterior surface of the abdominal aorta with partial destruction of the vertebrae enumerated in the pathologic diagnosis. Active syphilitic aortitis was recognized on gross and microscopic examination. There was a slight degree of stenosis of the orifice of the right coronary, the left appearing normal. Other than the stenosis that resulted from thickening of the aortic intima around the ostium, the coronaries appeared normal.

On histologic examination, the left coronary showed no abnormality, but the proximal 6 mm. of the right coronary was the seat of adventitial thickening, with an obliterating arteritis of the vasa, perivascular lymphocytic infiltration and small radial scars extending into the media.

Case 7.—A. G., a Negress, aged 55, died following a pulmonary hemorrhage from an abscess complicating organized lobar pneumonia. Her clinical history was negative so far as cardiovascular disease was concerned. The clinical diagnosis of syphilitic aortitis was made from the physical examination and from the ++++ Wassermann reaction.

The pathologic diagnosis was: organized pneumonia with multiple abscesses; pulmonary hemorrhage into the abscess cavity with free blood in the bronchi,

trachea, mouth and stomach; chronic syphilitic aortitis; fusiform aneurysm of the aorta; chronic syphilitic aortic valvulitis; stenosis of the ostia of the coronary arteries; cardiac hypertrophy, and arteriosclerosis.

The heart weighed 400 Gm. and, except for the hypertrophy, was essentially normal. The aortic ring measured 8.5 cm. in circumference, and the valve cusps were slightly thickened and rolled in, with beginning commissural separation. The aorta was moderately dilated in the ascending arch, and in the middle third there was a large saccular aneurysm. The intima of the entire aorta was thickened and puckered and contained hyaline plaques and vascularized depressed scars.

Both coronary orifices were stenosed, but they were still moderately patent. The stenosis was due entirely to intimal thickening around the ostia, and the vessels distal to the aorta showed no gross or microscopic evidence of syphilis.

Case 8.—J. J., a Negro, aged 37, entered the hospital in his fourth period of cardiac decompensation and died with a clinical diagnosis of syphilitic aortitis with valvular insufficiency, cardiac decompensation and bronchopneumonia. The Wassermann reaction of the blood was ++++. The autopsy confirmed the clinical diagnosis, and incidentally disclosed moderately severe stenosis of both coronary orifices due to the intimal proliferation and calcification in the aorta. As in the preceding case, the disease was limited to the ostia, the coronaries themselves showing no evidence of syphilis.

COMMENT

In six of the eight cases studied, the stenosis of the coronary arteries was due to, or contributed to by, syphilitic arteritis of their proximal portions. In none of these did the arteritis extend farther than the first 10 to 12 mm. of the vessel. In some, the stenosis was at the orifice, while in others the orifice was patent and the stenosis was distal to the aorta. Active syphilitic coronary arteritis was present with chronic inflammation of the aorta, and in some cases the coronary disease was chronic while the aortic syphilis was active. The coronary disease was not in all cases associated with syphilitic aortic valvulitis. The course of the coronary arteritis as hypothecated from a comparison of the mild with the severe pathologic changes indicated that the vascular change began in the adventitia as an obliterative endarteritis with perivascular infiltration of lymphocytes and plasma cells and medial damage, progressing from the periphery in toward the lumen of the vessel. Some of the arteries with these mild changes were stenosed at their orifices by proliferation of the aortic intima.

In cases in which the proximal extra-aortic portion of the coronaries was stenosed, the stenosis was due to intimal proliferation. In some instances, the proliferated intima had the appearance of well vascularized granulation tissue infiltrated by lymphocytes, and the media was disrupted by exudative, vascularized granulation tissue, with considerable thickening of the adventitia (fig. 7). The end-stage of this coronary endarteritis was thrombosis of the narrowed lumen with organization and, in some instances, calcification of the obliterating thrombus.

In cases 1, 2 and 3, the immediate cause of death appeared to be an obliterative coronary arteritis. All three patients died following sudden cardiovascular collapse characterized clinically as coronary disease. Two of these three had preceding anginal attacks. Electrocardiographic studies were not significant so far as coronary disease was concerned, and histologic studies of the myocardium failed to disclose evidence of infarction. It seems probable that in cases 1 and 3 there had developed a collateral circulation which by exclusion must have been either through the thebesian or through the aortic periadventitial vessels. The latter was deemed improbable because no periadventitial vessels of sufficient caliber to supply the heart were found in the ascending arch. In both of these there was almost complete obliteration of both coronary ostia, and this obliteration, as judged from the histologic study, was of considerable duration. The reason for the failure of this compensatory circulation after its apparent functional competency was not disclosed. In case 3 (fig. 9), the syphilitic inflammation was active with miliary gummas and excessive proliferation of granulation tissue, so that it seems possible for the obliteration of this vessel to have been an acute phenomenon. Injection of the left coronary artery in case 4 (fig. 10) indicated that the major coronary tree could be filled, although only the left orifice was patent and although the left descending ramus was thrombosed. The collateral circulation was adequate to fill the right coronary up to its obliterated orifice and to fill the recently thrombosed left descending branch below the point of obstruction. The injection mass, although too coarse to give capillary filling, was found free in the chambers, and no breaks in the continuity of the endocardium could be demonstrated. This observation was in accord with the investigations of Wearn [13] and was considered to indicate the patency of coronary-thebesian communications.

SUMMARY

Stenosis and obliteration of the proximal portions of the coronary arteries by syphilitic endarteritis frequently complicates syphilitic aortitis. The syphilitic inflammation of the coronary is not limited to that part of the artery included in the wall of the aorta. The coronary endarteritis occurs independently of aortic valvulitis and in some instances is the immediate cause of death without preceding cardiac decompensation. In two of the cases reported, the coronary stenosis was so complete and was of such long duration as to necessitate the hypothesis of a collateral blood supply, presumably through the thebesian vessels. The cause of the failure of the collateral circulation was not demonstrated.

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"MALIGNANT NEPHROSCLEROSIS" (FAHR) *

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The occurrence of cardiac hypertrophy in patients with contracted kidneys was recognized by Bright.[1] A causal relationship, however, between vascular alterations (arteriocapillary fibrosis) and "chronic Bright's disease" was first maintained by Gull and Sutton.[2] Years later, Ziegler [3] showed the dependence of some forms of renal atrophy on the arteriosclerosis of the renal arteries (arteriosclerotic contracted kidneys). He, however, still believed in the occurrence of a primary chronic interstitial nephritis with atrophy which he accepted to be the end-result of an inflammatory condition leading to a hyperplasia of the stroma. Jores [4] deserves the credit for having shown for the first time that such forms of renal atrophy, at that time commonly called chronic interstitial nephritis, were actually caused by arteriosclerosis of the smaller renal blood vessels. In Ziegler's form of renal arteriosclerosis, mainly the larger vessels were involved, though he mentioned the occasional occurrence of arteriosclerosis of the smaller vessels and even of the glomerular tufts. This distribution was bound to cause an irregular and focal type of cicatricial atrophy. According to Jores' [5] new conception, however, the diffuse fine granular kidney in chronic interstitial nephritis was also vascular, atherosclerotic in origin. This type of renal atrophy was always found combined with a marked hypertrophy of the left ventricle, and Jores pointed out that such cases were generally terminated by the vascular alterations (cardiac insufficiency or apoplexy). Furthermore, he gradually developed a point of view, already long held by Allbutt,[6] that the excessive cardiac hypertrophy might be

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* From the Laboratories of the Mount Sinai Hospital.

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5. Jores, L.: Ueber die Beziehungen der Schrumpfnieren zur Herzhypertrophie vom pathologisch-anatomischen Standpunkt, Deutsches Arch. f. klin. Med. **94**:1, 1908.

6. Allbutt, Sir Clifford: Diseases of the Arteries Including Angina Pectoris, London, The Macmillan Company, 1915, vol. 1.

produced by other than renal causes. Allbutt, recognizing the primary importance of hypertension in the causation of cardiac or cerebral failure, stressed the distinction between "Bright's disease" and another malady (hyperpiesia) which "abuts upon cardiac defeat or apoplexy, and does not at any stage, even of a fatal career, present uremic symptoms." He apparently did not recognize or include cases of primary hypertension with renal insufficiency. The old authors, however (Traube,[7] Bartels,[8] Delafield[9]), had not failed to emphasize that the fatal issue in patients suffering from genuine contracted kidneys or chronic interstitial nephritis was oftener determined by cardiac failure or cerebral accidents than by renal insufficiency, but nevertheless they looked on the kidneys alone as the seat and cause of the morbid process. It is clear that such diametrically opposed views led to much confusion and were the source of constant disagreement between pathologists and clinicians.

The strict clinical differentiation between primary hypertensive conditions existing with and without renal insufficiency and the recognition of pathologic criteria of two types of vascular renal disease corresponding to these two clinical forms were first established by Volhard and Fahr.[10] Whereas, only arteriosclerosis was supposed to be associated with the simple or benign hypertension, a combination of atherosclerosis with inflammatory renal changes was held to be responsible for a malignant form of hypertension, the "Kombinations Form." It was only logical to assume that this difference in morphology was the expression of a difference in etiology. Accordingly, a toxic factor was postulated by Volhard and Fahr which, superimposed on the atherosclerosis of the small vessels, produced the combination form.

Pathologists soon objected to this dualistic conception of vascular renal diseases. Thus, Paffrath[11] and Jores[12] assented to a differentia-

7. Traube, L.: Ueber den Zusammenhang von Herz und Nierenkrankheiten, Berlin, A. Hirschwald, 1856.

8. Bartels, C.: Handbuch der Krankheiten des Harnapparates, in von Ziemssen, H.: Handbuch der speciellen Pathologie und Therapie, Leipzig, F. C. W. Vogel, 1877.

9. Delafield, F.: On the Diseases of the Kidneys Popularly Called Bright's Disease, Lectures in the Practice of Medicine, New York, James T. Dougherty, 1904, pt. 4.

10. Volhard and Fahr: Die Bright'sche Nierenkrankheit, Berlin, Julius Springer, 1914.

11. Paffrath: Ueber die als "Kombinationsform" bezeichnete Nierenerkrankungen, Inaug. Diss., Marburg, 1916.

12. Jores, L.: Warum schreiben wir der Sklerose der Nierenarteriolen eine Bedeutung für das Zustandekommen gewisser Formen von Schrumpfnieren zu? Virchows Arch. f. path. Anat. **223**:233, 1917.

tion into two clinical forms, but maintained that the anatomic pictures are identical, varying the one from the other merely in extent and distribution of the atherosclerotic process involving the small vessels. They believed that in the pure hypertensive forms there existed only a focal involvement of the arterioles by atherosclerosis, whereas in the renal form there was a diffuse distribution of the same process. Löhlein [13] also, though recognizing the clinical distinction, did not see any essential morphologic and etiologic difference in the pathology. According to his conception, apparent variations in the histologic picture were explained adequately by differences in the severity of the atherosclerosis of the small vessels; and furthermore, the rate of development of this atherosclerotic process determined its severity. He wanted to designate this difference in degree and tempo by the terms arteriosclerosis initialis seu lenta et progressa. This term was not happily chosen. It enabled Fahr to point to the paradoxic fact that according to Löhlein's terminology the advanced lesions are found, as a rule, in younger persons, and the initial changes in the later phases of life. This relationship between the lesion and the age of the patient was clearly shown in Fahr's statistics and was confirmed by our material. In subsequent years, a number of papers from the clinical and pathologico-anatomic standpoints were published along the lines developed by Volhard and Fahr (Umber,[14] Rosenthal,[15] Herxheimer,[16] Machwitz and Rosenberg [17]). The clinicians generally accepted the dualistic conception of hypertensive disease. The anatomists, however, usually rejected the pathogenic separation of the renal lesions. The postulated inflammatory changes of the glomeruli in the combination form were the main point of disagreement. Since 1918 Volhard [18] has changed his ideas and no longer believes in the inflammatory nature of the glomerular and vascular changes. He now considers these lesions as the result of a prolonged

13. Löhlein, M.: Zur Pathogenese der vasculären Schrumpfniere, Med. Klin. **12**:741 and 872, 1916; Ueber Schrumpfnieren, Beitr. z. path. Anat. u. z. allg. Path. **63**:570, 1917; Erwiderung auf T. Fahr's Aufsatz, Centralbl. f. allg. Path. u. path. Anat. **28**:209, 1917.

14. Umber: Richtlinien in der Klinik der Nierenkrankheiten, Berlin. klin. Wchnschr. **47**:1261, 1916.

15. Rosenthal, K. O.: Zur Frage der benignen und malignen Arteriosklerose der Nieren, Deutsches Arch. f. klin. Med. **133**:153, 1920.

16. Herxheimer, G.: Nierenstudien I, Beitr. z. path. Anat. u. z. allg. Path. **64**:297, 1918.

17. Machwitz, H., and Rosenberg, M.: Zur Klinik der vasculären Schrumpfniere, Deutsch. med. Wchnschr. **42**:1188, 1916; Klinische und funktionelle Studien über Nephritis, München. med. Wchnschr. **63**:1285, 1916.

18. Volhard, F.: Die doppelseitigen hematogenen Nierenerkrankungen, Berlin, Julius Springer, 1918.

ischemia caused by a permanent vascular spasm. Fahr [19] also minimized the importance of the inflammatory glomerular alterations and instead stressed the inflammatory vascular damage. In a comprehensive article,[20] he emphasized far more the vascular lesions designated as necrotizing arteriolitis, productive endarteritis and periarteritis than the glomerular changes that serve as criteria in the differential diagnosis between benign and malignant nephrosclerosis. This emphasis on the significance of characteristic arterial lesions as a basis for the morphologic distinction and for the pathogenesis of vascular nephrosclerosis, with and without renal insufficiency, clears the way for a possible agreement between Fahr and his opponents. These (Herxheimer,[21] Stern [22] and Meyer [23] recognized the peculiar arteriolar necrosis in several cases with renal insufficiency as a factor for differentiation. On the other hand, there still exists a strong difference of opinion between Fahr and the opposite school in the matter of a specific etiology (syphilis, lead or articular rheumatism). However, some agreement has been reached: Herxheimer [24] recognized the possibility of a toxic damage superimposed on the original atherosclerosis leading to the severe picture of arteriolar necrosis. In this connection, it is well to remember that Löhlein, the strongest opponent of Fahr, recognized arteriolar necrosis and published an excellent picture of the condition.[25]

Within the last few years we have had the opportunity to observe a number of pertinent cases. We believe that a critical investigation of their clinical and anatomic features may still contribute some points to clarify the disputed problems of pathogenesis.

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19. Fahr, T.: Kurze Bemerkungen zur Frage der malignen Nierensklerose, Centralbl. f. allg. Path. u. path. Anat. **28**:408, 1917; Ueber maligne Nierensklerose (Kombinationsform), ibid. **27**:481, 1916; Ueber Nephrosklerose, Virchows Arch. f. path. Anat. **226**:119, 1919; Ueber atypische Befunde aus den Kapiteln des Morbus Brightii nebst anhangsweisen Bemerkungen zur Hypertoniefrage, ibid. **248**:323, 1924.

20. Fahr, T., in Henke and Lubarsch: Handbuch der speziellen pathologischen Anatomie und Histologie, Berlin, Julius Springer, 1925, vol. 6.

21. Herxheimer, G.: Ueber Arteriolonekrose der Nieren, Virchows Arch. f. path. Anat. **251**:709, 1924.

22. Stern, M.: Ueber einen besonders akut verlaufenen Fall von Arteriolonekrose der Nieren mit dem makroskopischen Bilde der "Grossen bunten Nieren," Virchows Arch. f. path. Anat. **251**:718, 1924.

23. Meyer, O.: Ueber die Veränderungen und Bedeutung entzündlicher Gefässveränderungen in der Nieren mit besonderer Berücksichtigung der Glomerlitis der sekundären und genuinen Schrumpfnieren, Verhandl. d. Deutsch. path. Gesellsch. **19**:352, 1923.

24. Herxheimer, G.: Krankheitslehre der Gegenwart, Leipzig, Theodor Steinkopf, 1927, p. 182.

25. Löhlein (footnote 13, second reference).

MATERIAL AND METHODS

Our material consists of cases that in clinical course and pathologic picture conform with the diagnostic criteria of "malignant nephrosclerosis." In addition, we have examined a considerable number of cases of simple benign sclerosis, three cases of periarteritis nodosa and cases of subacute glomerulonephritis with severe vascular lesions; we have also studied ample control material dealing with various questions of vascular pathology. Paraffin as well as frozen sections were used. The former were examined in long serial sections in order to obtain information about the status of the various portions of the vascular tree in the renal cortex. Various staining methods were employed, including the methods recommended by McGregor [26] for minute study of the glomeruli. Because of the similarity of the cases in clinical and anatomic aspects we shall describe in detail only a few typical cases and supply short notes on the others.

REPORTS OF CASES *

CASE 1.—*History.*—M. F., a white man, aged 29, married, a garage manager, was first admitted to Mount Sinai Hospital on June 18, 1929. His mother had died of gallbladder disease. His father, three brothers, one sister and two maternal aunts, who were living and well, showed normal blood pressure and normal hearts. The patient had been married four years and had one child, aged 2½ years. His wife never had had a miscarriage.

As a child he had had mumps. Eight years before admission to this hospital he had had his tonsils removed; six years later, he had had an appendectomy for acute appendicitis, and at this time his blood pressure was found to be 140 mm. of mercury. Four years before admission, he began to have headaches two or three times a month. In August, 1928, the headaches became more severe and localized above the eyes and in the region of the temples. On advice of a doctor, the septum was corrected, but without relief. In October of the same year, he applied for life insurance and was refused because of high blood pressure (170 mm. of mercury).

The headaches became continuous and severe, and on March 26, 1929, after having consulted many physicians, who treated him for sinus disease, he went to the hospital of the Rockefeller Institute, where he stayed until May 10. On admission there, his blood pressure was 240 systolic and 140 diastolic; it gradually fell to 215 systolic and 145 diastolic. Following a rather large hemorrhage from the rectum, the blood pressure fell to 155 systolic and 105 diastolic, but gradually rose again until at the time of his discharge from that hospital it was 180 systolic and 125 diastolic. Chemical examination of the blood at this time showed 22.7 mg. of urea and 32 mg. of nonprotein nitrogen per hundred cubic centimeters of blood. No dilution or concentration tests were done. The phenolsulphonphthalein excre-

26. McGregor, L.: The Finer Histology of the Normal Glomerulus, Am. J. Path. **5**:545, 1929.

* Drs. G. Baehr, L. Kessel, B. S. Oppenheimer and I. Strauss permitted us to use the clinical data in these cases, and Dr. R. L. Cecil, some of the clinical data in case 2.

tion was 60.3 per cent after two hours. The result of the urea clearance test (van Slyke index) was 45 per cent of normal. The diagnosis was: arterial hypertension and chronic sinusitis. The patient was restricted to a low protein and salt diet, and thereafter felt better.

Because it was thought that the hypertension might be due to the sinus infections he was admitted to the New York Eye and Ear Infirmary, where a radical operation was performed on the right antrum. He had no relief from his headaches. On June 18, he fainted and was taken to Mount Sinai Hospital for observation.

Examination.—The patient was an afebrile, poorly nourished young man, who had lost about 50 pounds (22.7 Kg.) within the last year. The heart was slightly enlarged to the left; the sounds were regular and strong. The blood pressure was 230 systolic and 172 diastolic. The eyegrounds on both sides revealed neuroretinitis.

The specific gravity of the urine was 1.010; a trace of albumin was shown; the sediment contained hyaline casts and a few red and white blood cells. The result of the concentration test was from 1.012 to 1.014. The phenolsulphonphthalein excretion was 57 per cent after two hours. Chemical examination of the blood showed: urea nitrogen, 14 mg.; uric acid, 1.6 mg.; cholesterol, 162 mg., and sugar, 79 mg., per hundred cubic centimeters of blood. The Wassermann reaction was negative. The blood count gave: hemoglobin, 102 per cent; red blood cells, 4,800,000, and white blood cells, 13,000, with polymorphonuclear leukocytes, 83 per cent, and lymphocytes, 17 per cent.

Course.—During his stay in the hospital, the patient had a short attack of dizziness. A tentative diagnosis of malignant hypertension without nitrogen retention, with inability to concentrate the urine, was made. After a week the patient left the hospital and was admitted to Montefiore Hospital, as having a chronic case, for further study. There he stayed until August, 1929, without any change in his condition and without any new developments in the results of the laboratory tests. After leaving Montefiore Hospital, he was apparently better for two weeks; then his headaches recurred with great intensity. He became somewhat dyspneic and restless and vomited several times. He also noticed some diminution of vision and had many episodes of blurring.

On September 30, he again entered Mount Sinai Hospital. He was afebrile, drowsy and apathetic, and complained of severe headache. The breath was foul, but not urinous. The fundus presented marked hypertensive retinitis. The heart seemed slightly enlarged to the left. The second aortic was greater than the second pulmonic sound. There was a systolic murmur behind the middle of the sternum and over the aortic area and a systolic blow over the apex. No pericardial rub was heard.

On October 1, the blood pressure was 188 systolic and 134 diastolic. Chemical examination of the blood showed: urea nitrogen, 14 mg.; creatinine, 1.5 mg.; uric acid, 2.8 mg.; cholesterol, 248 mg., and sugar, 98 mg. On October 2, the result of the concentration test was from 1.010 to 1.016. The urine showed abumin (++), many hyaline and granular casts and sparse red and white blood cells. For two weeks the condition remained the same.

On October 14, edema of the lower lids was noted. The urine showed increased albumin and for the first time the guaiac reaction was positive. Chemical examination of the blood showed 30 mg. of urea nitrogen. In the evening, the patient suddenly became delirious, completely disoriented and uncontrollably restless. Under markedly increased tension, 50 cc. of clear fluid was withdrawn

from the spinal canal. An intravenous injection of 2 cc. of diallyl-barbituric acid was without effect, but after 8 minims (0.5 cc.) of Magendie's solution was added, the patient became quiet. Within the next weeks, the blood pressure remained high, and precordial pains began. The urea nitrogen of the blood rose to 44, 57 and 109 mg. per hundred cubic centimeters. On November 30, a loud friction rub was heard over the pericardium. The liver was enlarged and tender. Muscular twitchings developed, and the patient became stuporous. He died on December 7, sixty-eight days after his second admission and fifty-three days after urea retention had been ascertained the first time.

Necropsy.—Necropsy was performed by Dr. Otani twelve hours later. The body was that of a poorly nourished white man in complete rigor mortis. The mucous membranes were pale and slightly cyanotic. No jaundice, petechiae or edema was present.

The lower lobe of the left lung showed a few scattered areas of grayish infiltration. The trachea and the larger bronchi were congested and contained mucopurulent exudate.

The heart with the ascending aorta weighed 550 Gm. The pericardial surfaces were dull, showed injection and were covered with fibrin. The left ventricular wall was enlarged, measuring as much as 3 cm. on cross-section. The valves were thin and closed well. The pulmonary artery was smooth. The aorta showed a few scattered yellowish flecks in the intima, but was elastic. The coronary arteries also showed a few lipoid deposits in the intima, but no narrowing. The myocardium of the left ventricle was yellowish gray.

The kidneys weighed 120 Gm. each. They measured 11 by 5 by 3 cm. The capsules stripped easily, revealing a grayish brown-red surface. The red color was more prominent on the convexity, whereas the anterior and posterior surfaces appeared more grayish brown. The red portions were slightly depressed, and the surface was accordingly slightly granular like Scotch grain leather. There were numerous sharply circumscribed hemorrhages varying in size from that of a pinpoint to that of a pinhead. On section, the cortex was of equal width and sharply demarcated from the medulla. The regular markings were somewhat indistinct because of numerous irregular grayish flecks and larger, more sharply outlined dark red areas. Occasional hemorrhages like those on the surface were seen. The medula showed radial striae running toward the papillae. The pelvis had numerous confluent hemorrhages. The intima of the renal artery was smooth. The kidneys are shown in figures 1 and 2.

Microscopic examination showed the surface of the kidneys to be slightly irregular; the capsule was neither thickened nor infiltrated by cells. On examination of the cortex under very low power magnification, the cortical structure was seen to be altered by a widespread increase in the stroma. The loose connective tissue infiltrated the parenchyma, separating and compressing the convoluted tubules, which only rarely formed islands where canaliculi were close to each other (fig. 3). The stroma was slightly infiltrated by lymphocytes, polymorphonuclear leukocytes, polyblasts and plasma cells. It contained a great number of dilated and engorged capillaries. The tubules often showed marked alterations. A great number, though separated by connective tissue strands, still retained their topographic histologic characteristics, but were dilated and contained hyaline casts, epithelial cells and débris, and red and white blood cells. Others, however, had an atrophic epithelial lining containing fat droplets, which were often doubly refractile, and hyaline droplets. The medulla showed a moderate increase in the stroma; the tubuli recti contained desquamated cells, cellular débris and hyaline casts. On examination of the malpighian corpuscles, one was surprised to find that only a

small number showed readily recognized damage as, for example, hyalinization (fig. 3). The majority under low magnification appeared unaltered, except that their capillaries were completely or partially bloodless and were conspicuously small.

On higher magnification, one recognized a collapse of many tufts. The basal membrane of the capsule often showed slight hyalinization, and the external epithelial layer was occasionally conspicuous owing to an increase in the number of cells, which rarely contained fat but occasionally contained hyaline droplets. The changes of the internal epithelial layer in a relatively small number of glomeruli were far more conspicuous. They consisted in a multiplication of the

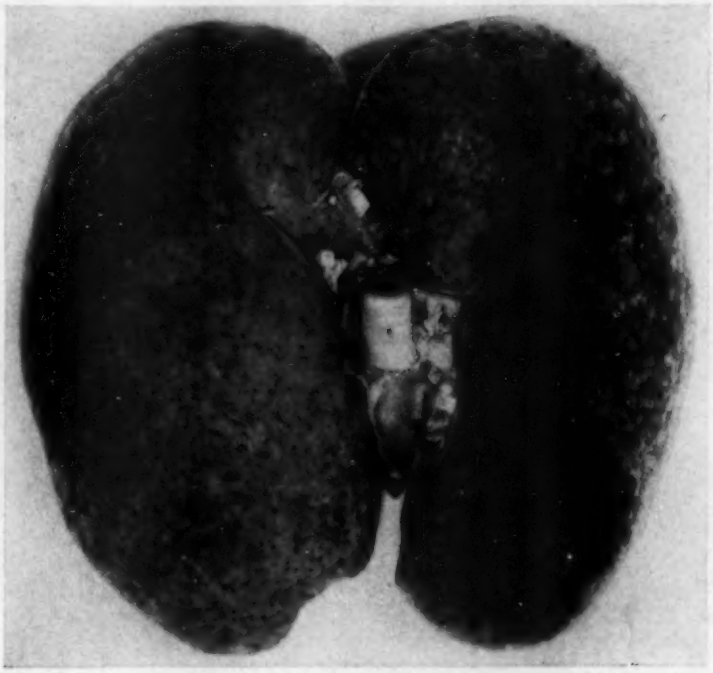

Fig. 1 (case 1).—A kidney showing diffuse flat granulation but only slight decrease in size. Note the numerous hemorrhages.

cells covering the collapsed capillary loops, with frequent hyaline droplet degeneration and accumulation of isotropic and anisotropic fat droplets. Sometimes the entire glomerulus was infiltrated with fat. In paraffin sections, such loops were thickened and homogeneous and contained many vacuoles. The endothelial nuclei were pale, small and often broken up. The epithelial cells were large and swollen, frequently showing severe hyaline droplet degeneration and necrosis. The lumen of such capillaries was often thrombosed. Fusion of loops to each other and the capsule was not uncommon. The "arcuate arteries" and the large proximal branches of the interlobular arteries showed marked thickening of the intima. The media was often compressed. The internal elastic membrane was separated into several layers, between which there was a more or less cellular connective tissue. This showed a moderate number of fat droplets within and

between the fibroblasts. The adventitia was free from cellular infiltration. The more peripheral portions of the interlobular arteries showed an extreme degree of narrowing of the lumen caused by a proliferation of the subendothelial intimal layer, which formed a moderately cellular connective tissue with abundant fat infiltration. Lamellation of the internal elastic layer was less distinct in the peripheral portions of the vascular tree. The arteriolar endings of the interlobular arteries and the vasa afferentia showed diffuse fat infiltration and hyalinization with frequent nuclear disintegration, hemorrhagic infiltration of the wall, aneurysmic dilatation and perforation, and perivascular hemorrhage. Never, however, was infiltration with polymorphonuclear leukocytes or other inflammatory cells seen.

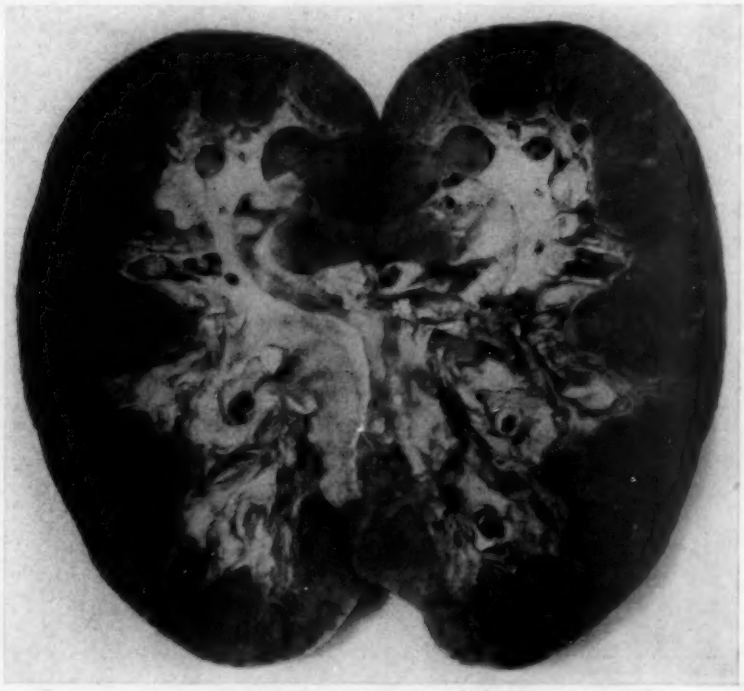

Fig. 2.—Cross-section of the kidney shown in figure 1, showing the diffuse grayish infiltrations that obscure the cortical markings.

The heart showed fibrinous pericarditis. There were no changes in the arteries. Hypertrophy of muscle fibers was found.

The lung showed focal pneumonia. There was no excessive number of pigment cells. The alveolar septums were not thickened, and there was no evidence of chronic congestion.

The spleen disclosed considerable atherosclerosis of the larger vessels and a moderate degree of hyalinization of the arterioles.

The liver disclosed slight atherosclerosis of the larger vessels and insignificant hyalinization of the arterioles.

The pancreas presented moderate atherosclerosis and hyalinization of arterioles.

In the stomach and intestines, the arteries were normal.

The prostate and seminal vesicles showed severe atherosclerosis of the larger arteries and hyalinization of the arterioles.

In the muscle and skin, the arteries were normal.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; fibrinous pericarditis; acute hemorrhagic bronchitis; bronchopneumonia of the left lower lobe; hypertrophy of the median lobe of the prostate, and hypertrophy and dilatation of the bladder.

CASE 2.—*History.*—H. G., a white man, aged 42, married, a metal worker, was admitted to Mount Sinai Hospital on Aug. 7, 1928. The family history was

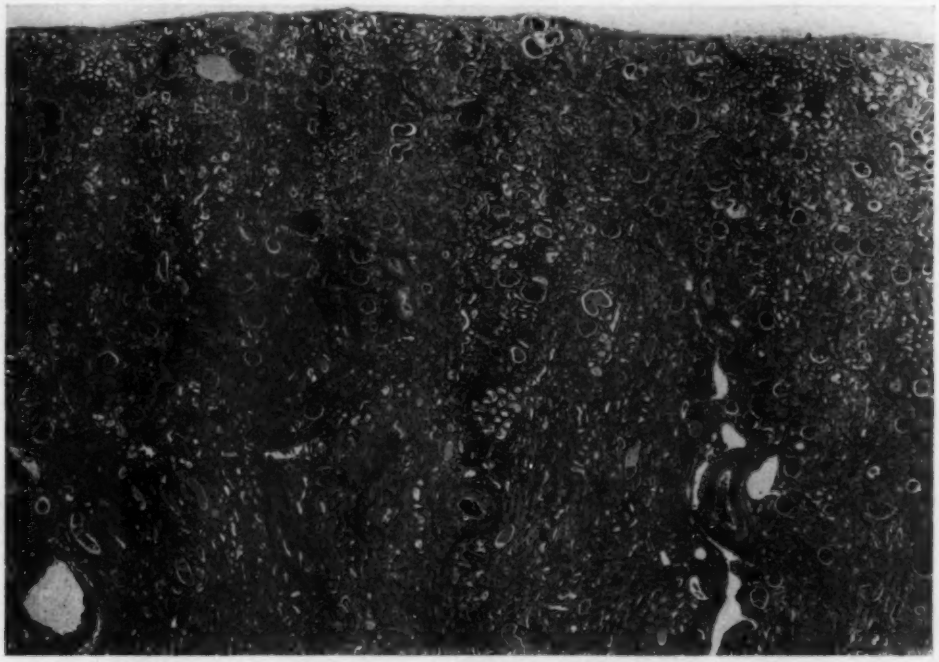

Fig. 3 (case 1).—Low power view of the cortex showing the alteration of the normal structure: increase in the stroma, separation and atrophy of the tubules, but only sporadic hyaline glomeruli.

unimportant. The patient had measles as a child and diphtheria in 1916. He had not had scarlet fever, rheumatism or frequent sore throats. He used no alcohol; he smoked cigarets.

Three and one-half years before admission to the hospital, he was refused life insurance because of high blood pressure. At this time he had dyspnea and was examined at Cornell Clinic. The blood pressure was 178 systolic and 110 diastolic. The specific gravity of the urine was 1.028. No albumin or sugar was found. The result of the concentration test was from 1.021 to 1.031. The phenolsulphonphthalein excretion was 45 per cent after two hours. The diagnosis was: essential hypertension.

Two years before admission, the blood pressure was 200 mm. of mercury. Occasional ringing was present in the ears. In March, 1927, the blood pressure was 235 mm. of mercury. At this time, sugar was found in the urine. The patient was put on a restricted diet, and the sugar disappeared. He had no polyuria. He received iodine, but this treatment was discontinued because of swelling of his neck. About eleven weeks before admission, his doctor noticed that the liver was enlarged and tender and that the heart was large. For ten weeks the patient had been suffering from attacks of dyspnea. He lost 28 pounds (12.7 Kg.). Digitalis was given. Because of his symptoms he was admitted to the hospital.

Examination.—The patient was afebrile. The blood pressure on admission was 220 systolic and 100 diastolic; during the next month it was between 220 systolic and 110 diastolic and 266 systolic and 135 diastolic. The left side of the heart was markedly enlarged. The fundi showed progressive neuroretinitis.

The urine showed albumin, many white, and rare red blood cells, and granular casts. The specific gravity was fixed at from 1.006 to 1.010. The phenolsulphonphthalein excretion after two hours was 10 per cent. The urea nitrogen of the blood, on admission, was 47 mg. per hundred cubic centimeters. Uric acid was 4.2 mg. The Wassermann reaction was negative. The blood count gave: hemoglobin, 50 per cent; red blood cells, 2,600,000, and white blood cells, 9,800. The differential count gave: polymorphonuclear leukocytes, 79 per cent; lymphocytes, 21 per cent; mononuclears, 6 per cent; eosinophils, 1 per cent, and basophils, 1 per cent.

Course.—On August 18, the patient began to vomit, and displayed general nervousness and anxiety. He suffered from precordial pain. The urea nitrogen of the blood was 78 mg. On September 7, there was a pericardial friction rub. The urea nitrogen of the blood was 106 mg. On September 10, there was uncontrollable vomiting. The urea nitrogen of the blood was 206 mg. The patient showed extreme emaciation. There were signs of bronchopneumonia in the left lower lobe. On September 12, the patient died. The clinical diagnosis was: chronic glomerulonephritis with hypertension, pericarditis and uremia.

Necropsy.—Necropsy was performed by Dr. Klemperer on the day of death. The kidneys weighed 120 Gm. each, and measured 11 by 5 by 3 cm. They had a slightly granular surface and were a mottled grayish brown-red. They were firm. Numerous small hemorrhages were seen. The cortex was of normal width, and its markings were somewhat indistinct. The renal artery was very thick, as were also its ramifications.

Microscopic examination of the kidneys showed: considerable increase in stroma; partial obliteration of cortical structure due to extensive tubular atrophy; insignificant glomerular fibrosis with diffuse capillary collapse; focal degeneration and proliferation of glomerular epithelium; occasional necrosis of capillary tufts and hemorrhagic infarction of the glomeruli; diffuse intimal proliferation within the entire vascular tree of the cortex, with elastica lamellation and fatty infiltration of the intima; excessive fatty changes and occasional necrosis of the arterioles without inflammatory reaction; an extreme degree of stenosis, and an occasional complete closure of small arteries and arterioles.

The heart presented severe myocardial fibrosis and recent myomalacia with lymphocytic infiltration. There was severe sclerosis of the coronary artery. The small intramyocardial branches were not involved. The aorta showed severe atherosclerosis.

Atherosclerosis of the arteries and hyalinization of the arterioles was shown to a marked extent by the pancreas, and the suprarenal glands, to a moderate extent by the spleen and to a slight extent by the stomach and intestines.

The choroid showed extreme intimal proliferation of the small arteries.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; coronary closure (right posterior descending ramus); acute fibrinous pericarditis; hypertrophy of the left and right ventricles; myocardial fibrosis; atherosclerosis of the aorta; focal pneumonia of both lower lobes; and left hydrothorax.

CASE 3.—*History.*—S. T., a white boy, aged 8½ years, was admitted to Mount Sinai Hospital on June 14, 1928. The family history was irrelevant. The patient had had whooping cough, pneumonia and measles. At the age of 3, he had suffered from nausea, vomiting, chills and convulsions for two weeks. The condition was diagnosed as ptomaine poisoning. There had been a second attack, but the date of this could not be ascertained. The patient had frequent colds. Within the last year, he became dyspneic on exertion. About three months prior to admission, it was observed in school that the child had difficulty with his eyesight. The diminution of vision was progressive. Severe headaches set in. On May 28, ophthalmologic examination revealed early retinitis. On June 6, the urine gave a strongly positive reaction for albumin. The blood showed: urea nitrogen, 67 mg.; uric acid, 7.2 mg.; creatinine, 1.5 mg., per hundred cubic centimeters. In the last three weeks before admission, he vomited several times.

Examination.—On admission, the patient was subacutely ill, but afebrile. He was not irrational, but acted queerly. There was a uriniferous odor of the breath. The heart was not enlarged. The second aortic beat was accentuated. The fundi showed extensive neuroretinitis with bilateral detachment of the retina. The blood pressure was 235 systolic and 175 diastolic.

The result of analysis of the urine for albumin was strongly positive; there were granular casts. The specific gravity was from 1.002 to 1.008. The phenolsulphonphthalein excretion was represented only by traces. The urea nitrogen of the blood was 56 mg. on admission, rising within the next few weeks to 110 mg. to reach finally 235 mg. per hundred cubic centimeters. Uric acid was 5.5 and 9.3 mg.; cholesterol, 260 and 290 mg. The Wassermann reaction was negative. The blood count gave: hemoglobin, 62 per cent; red blood cells, 3,510,000, and white blood cells, 11,800.

Course.—During his stay in the hospital, the child was drowsy, had severe headaches and was nauseated. He had epistaxis, and he lost a great quantity of blood by rectum. He went gradually down hill. General convulsions developed. Within the last thirty hours, complete anuresis existed. Small purpuric spots developed. He died three weeks after admission.

Necropsy—Necropsy was performed fourteen hours later by Dr. S. Otani. The kidneys weighed 60 and 40 Gm., respectively. One was 7 by 4 by 1.5 cm., and the other was 6 by 3 by 1.5 cm. in size. The surfaces showed diffuse flat granular elevations of irregular size. The color was brownish red. Numerous petechial hemorrhages were seen on the surface, and on cross-section. The cortical markings were indistinct; the separation of cortex and medulla was not sharp. The blood vessels were slightly thickened.

Microscopic examination revealed diffuse increase of the stroma and focal infiltration with lymphocytes and fibroblasts. No fat was seen. Numerous smaller and larger anemic infarcts were seen, with complete necrosis of tubules and glomeruli and infiltration with polymorphonuclear leukocytes; there was congestion at the periphery. The convoluted tubules, for the most part, were separated by the increased

interstitial tissue and were atrophic, with noncharacteristic epithelial lining. There were only occasional islands of normal tubules. The lumen contained albumin, many desquamated epithelial cells and in the vicinity of infarcts polymorphonuclear leukocytes. Henle's loops and the secondary convoluted tubules contained fibrin, cellular casts and rarely hyaline cylinders and red blood cells. The epithelial cells of the normal tubules contained fat droplets, occasionally doubly refractile crystals; they frequently showed hyaline droplet degeneration. The majority of the glomeruli were small, with the capillary loops collapsed and bloodless. There were a few fibrosed glomeruli, but more frequently there were all stages of homogeneization and fusion of capillary loops, with gradual disappearance of the nuclei. Epithelial proliferation was frequent, with presence of hyaline droplets and fat within these cells. Sporadically, an accumulation of polymorphonuclear leukocytes within the still permeable capillaries was found in the vicinity of the severely damaged loops. Occasionally, necrosis of the tufts was found at the hilus, as well as within the center, extending from the afferent vessel to the capillaries. Here and there were hemorraghic infarctions of entire glomeruli. Frequent necrosis of the hyalinized vasa afferentia was observed, with extreme narrowing of the lumen or complete closure by small hyaline thrombi without perivascular cell infiltration. The most marked narrowing of the lumen of the interlobular arteries was caused by a cellular intimal proliferation with almost complete obliteration. Sudan stain showed a concentric accumulation of fat in the deeper layers of the intima adjacent to the compressed media and a complete infiltration of the wall of the smallest hyalinized and necrotic vessels with fat. Within the arcuate arteries and proximal portions of the interlobular arteries elastica lamellation was seen; within the smaller branches, only occasional elastica new formation. Of the other organs, only the spleen, pancreas and suprarenal capsule showed moderate hyalinization of the arterioles. The choroid showed extreme intimal proliferation of the small arteries and marked hyalinization and fatty changes of the arterioles.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the heart, particularly of the left ventricle; acute hemorrhagic enterocolitis with ulcerative proctitis, and atherosclerosis of the descending aorta and coronary arteries.

Case 4.—*History.*—A. G., a white man, aged 29, engaged in the clothing business, was admitted to Mount Sinai Hospital on Dec. 9, 1928. The history was irrelevant. The patient had not had scarlet fever or rheumatic fever. He gave no history of having had venereal diseases. He had always been well, except for occasional sore throats and colds. A few weeks before admission, he noticed frequency of urination during the night. He consulted a physician, who found an elevation of the blood pressure. At the same time, he suffered from suboccipital and frontal headaches. He lost appetite and became weak, and for the last few days before admission he was in bed. During the latter period, he had vomited once, but was not drowsy. Occasional twitchings of the muscles of the legs occurred. For these reasons he was admitted to the hospital.

Examination.—The patient impressed one as being chronically ill; he was emaciated and afebrile. The apex of the heart was in the fifth interspace, 10 cm. from the midline. The fundi showed intense acute neuroretinitis superimposed on a chronic rĕtinitis. In places the arteries were obliterated, in places thrombosed. The spinal fluid was under increased pressure. On an average of eight readings, the blood pressure was 227 systolic and 139 diastolic.

The urine contained albumin, sediment, hyaline and granular casts and a few red blood cells. The concentration test showed the specific gravity of the urine

fixed at 1.008. The urea nitrogen of the blood, on an average of five examinations, was 29 mg.; the uric acid, 3 mg. and the creatinine, 3.6 mg. The Wassermann reaction was negative. On an average of three examinations, the hemoglobin was 50 per cent. The red blood cells numbered 3,620,000 and 3,020,000; the white blood cells, 8,800, with polymorphonuclear leukocytes, 40 per cent, lymphocytes, 56 per cent, mononuclears, 3 per cent, and eosinophils, 1 per cent.

Course.—The patient continued to have sévere headaches and vomited profusely. He contracted pneumonia and died in pulmonary edema on Dec. 27, 1928.

Necropsy.—Postmortem examination was made by Dr. Otani the next day. The heart weighed 520 Gm. The right kidney weighed 120 Gm.; the left, 100 Gm. There were diffuse irregular, flat granulations of the surface. The color was brownish red, and there were many pinpoint-sized hemorrhages. The cortical markings were indistinct, owing to diffuse grayish streaks and points and occasional hemorrhages.

Microscopically, the kidneys showed marked increase in the stroma, numerous small anemic infarcts, interstitial infiltration with lymphocytes and leukocytes and congestion. The convoluted tubules were partly arranged in larger islands; a greater part, however, were separated by the stroma proliferation and were often atrophic. There were foci of conspicuous dilatation. There was fatty and hyaline droplet degeneration of the epithelium. The lumen contained cellular débris, occasionally blood, and within Henle's loops, occasional calcium casts. The majority of the malpighian corpuscles were conspicuously small, their capillaries empty and collapsed. Only a few completely hyalinized glomeruli were found; more frequently they showed various phases of developing fibrosis. Occasional advanced fatty changes and necrosis of capillaries were noted, with accumulation of leukocytes within adjacent loops. Occasional epithelial proliferation with fatty and hyaline droplet degeneration was observed. There occurred extreme fatty metamorphosis of arterioles with occasional hemorrhagic infiltration of the wall and nuclear disintegration. There was no perivascular cell infiltration. Also the interlobular arteries showed severe intimal degeneration with occasional necrosis and thrombosis, as well as extreme narrowing of their lumen by cellular intimal proliferation with fine fat droplets within the external layers, but no inflammatory cells. Distinct elastic hyperplastic thickening of the intima of the "arcuate arteries" was seen, and insignificant elastica lamellation farther distally.

Of other parts of the body, the spleen, pancreas, prostate, suprarenal glands and intestine showed moderate hyalinization of the arterioles.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; atherosclerosis of the descending aorta and peripheral arteries; bronchopneumonia (left lower lobe); chronic calcified tuberculosis of the right upper lobe, tracheobronchial lymph nodes, spleen and liver; right pleural adhesions.

CASE 5.—*History.*—D. S. J., a white man, aged 41, a worker in a garage, married, was admitted to Mount Sinai Hospital on March 12, 1928. The family history was of no importance. In childhood the patient had not had scarlet fever, rheumatic fever or any other diseases. He said that he had not contracted any venereal diseases, but his wife had had one miscarriage and two of their children were dead; the third was living and well. Ten years before admission, the patient began to have headaches, mainly in the back of the head; they were intermittent. Six years before, high blood pressure was detected; the patient had his teeth extracted and adopted a meat-free diet. Later his headaches became severe.

There was cloudiness of vision for four months. At the time of examination, he was unable to distinguish faces clearly.

Examination.—On admission, the patient was irrational, with twitchings of the hands, chronically ill and afebrile. The heart was enlarged. On an average of six readings, the blood pressure was 200 systolic and 148 diastolic, the pressure going down from 238 systolic and 180 diastolic to 144 systolic and 106 diastolic in the last days. The fundi showed neuroretinitis with hemorrhage.

Examination of the urine showed oliguria, albumin +++, and in the sediment hyaline and granular casts. A concentration test showed the specific gravity to be from 1.010 to 1.020. The urea nitrogen of the blood was from 40 to 71 mg.; the uric acid, from 4.6 to 6 mg., and the cholesterol, from 280 to 346 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed: white blood cells, 10,000, with polymorphonuclear leukocytes, 85 per cent, lymphocytes, 8 per cent, mononuclears, 4 per cent, and eosinophil leukocytes, 3 per cent.

Course.—The patient became psychotic, contracted bronchopneumonia and died on March 19, one week after admission.

Necropsy.—Necropsy was performed eight hours later by Dr. Otani. The kidneys weighed 170 Gm. each and measured 10 by 5 by 3 cm. They were identical in appearance with those described in the previous cases. Numerous hemorrhages were presented.

Microscopic examination revealed only moderate focal increase in the stroma. The capillaries were congested. There was edema of the interstitial tissue. Fine fat droplets with a few doubly refractile bodies were noticeable within the interstitium. The tubules were generally well preserved and closely arranged, except within the areas of fibrosis. There was much fat and hyaline droplet degeneration. The glomeruli were anemic; very few were hyalinized. Frequent epithelial proliferation and severe degeneration were noted. Fatty changes and necrosis of capillary loops were present. Severe fatty metamorphosis of arteriolar walls was observed, with necrobiosis and hemorrhagic infiltration. There were no inflammatory cells around. There was extreme narrowing of interlobular arteries by cellular intimal proliferation with much fat. Moderate elastica lamellation occurred within the proximal portions of the interlobular arteries (figs. 4 and 5).

Examination of the vessels in other organs showed: hyalinization of arterioles in the spleen and the pancreas; changes in two arteries of the testis similar in intensity to those found in the interlobular arteries, but with distinct elastica lamellation; advanced atherosclerosis of branches of the coronary arteries, and extreme intimal proliferation of the small arteries and hyalinization of the arterioles of the choroid. The retina showed many hemorrhages and areas of severe degeneration.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; concentric hypertrophy of the heart, especially of the left ventricle; atherosclerosis of the aorta and of the coronary and cerebral arteries; hemorrhagic tracheitis and bronchitis, and bilateral bronchopneumonia of the lower lobes.

Case 6.—*History.*—L. G., a white woman, 42 years of age, married, a housewife, was admitted to Mount Sinai Hospital on March 8, 1928. The mother died of high blood pressure; the father, of heart trouble. The patient stated that she had not had scarlet fever, diphtheria, rheumatic fever, venereal disease or any other illness. She had had one miscarriage and one stillbirth. Six months before admission, she had nosebleed; she was told that she had high blood pressure and

kidney disease. For several months she had swollen ankles, breathlessness with palpitation on exertion, and had seen spots before the eyes. These symptoms became severe within the last few days before her admission to the hospital.

Examination.—The patient was pale, with puffy eyelids, slightly dyspneic and afebrile. She had fine twitchings of the hands and fingers, slight exophthalmos and a subicteric tint of the sclerae. The thyroid gland was not felt. The heart was markedly enlarged. There was slight edema of the lower extremities. She was disoriented. The fundi showed neuroretinitis and atherosclerosis. On an average of three readings, the blood pressure was 190 systolic and 110 diastolic.

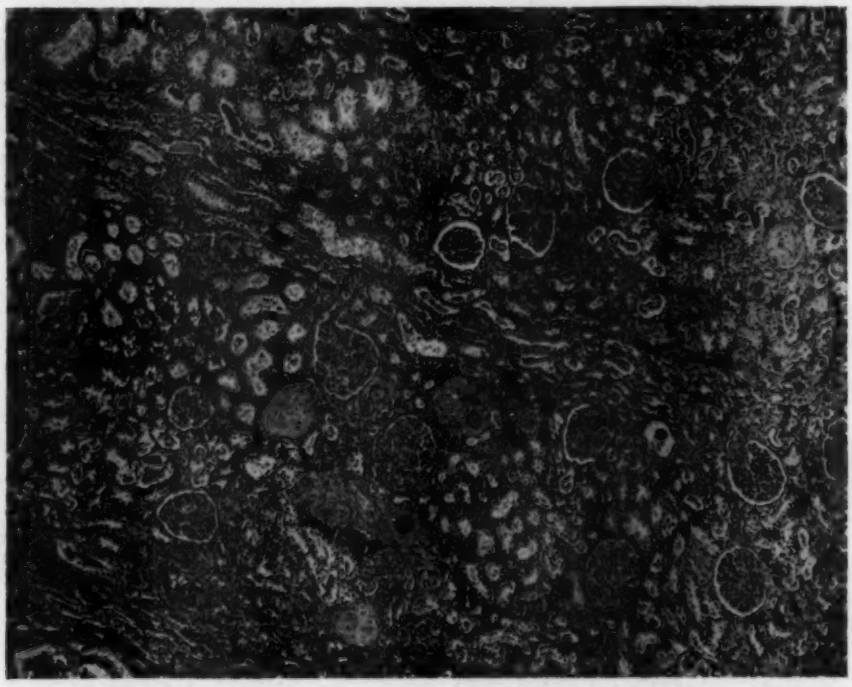

Fig. 4 (case 5).—Section showing the very moderate increase in the stroma, the absence of conspicuous tubular alteration or glomerular hyalinization, the anemic glomeruli with collapsed capillaries, the extreme constriction of the interlobular arteries and the severe hyaline and fatty change of the arterioles.

The amount of the urine could not be ascertained because of incontinence. The albumin was +++; the sediment contained granular casts; the specific gravity was 1.006. The urea nitrogen of the blood was from 82 to 112 mg.; the uric acid, from 6.3 to 7.5 mg., and the creatinine, from 4.4 to 9.5 mg., per hundred cubic centimeters. The Wassermann reaction was twice negative. The blood count gave: hemoglobin, 50 per cent, and white blood cells, 10,000, with polymorphonuclear leukocytes, 81 per cent, lymphocytes, 14 per cent, and mononuclear cells, 5 per cent.

Course.—The patient went rapidly down hill, and died on March 16, eight days after admission.

Necropsy.—Two hours later, postmortem examination was made by Dr. Otani. The kidneys weighed 110 Gm. each. They were of the same granular appearance as that described in the previous cases. The surface was sprinkled with numerous hemorrhages (fig. 6), which appeared also in the cross-section.

Microscopic examination showed the stroma of the kidneys to be increased almost throughout. There were few areas where the tubules were closely packed; generally a loose connective tissue separated them. It was densely infiltrated by lymphocytes mingled with occasional plasma cells and polymorphonuclear leukocytes. The capillaries were congested. In numerous places there was extensive hemorrhage, the origin of which could be traced only in complete serial sections.

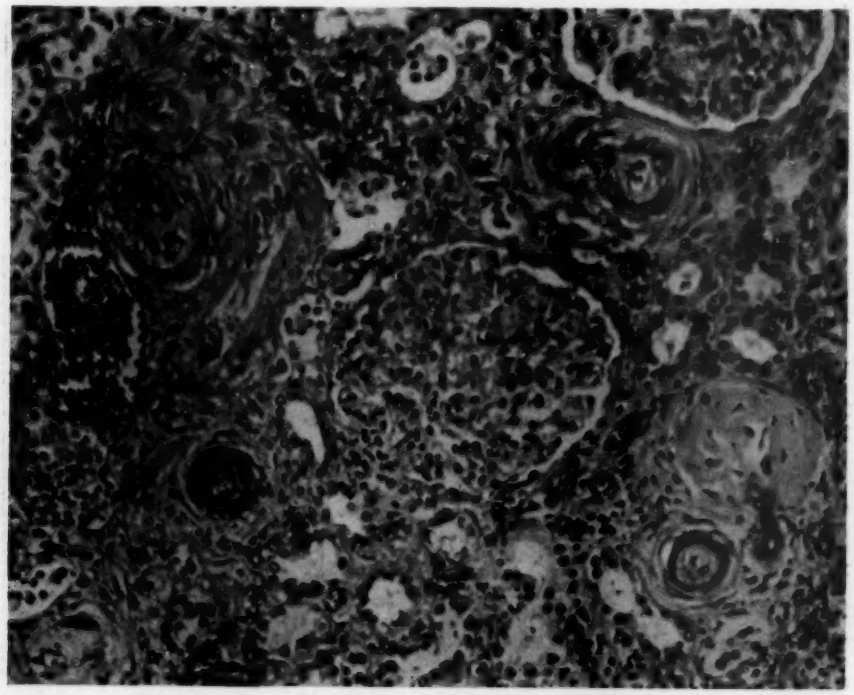

Fig. 5.—Higher magnification of the upper central part of the same section.

The hemorrhages were due to rhexis of small necrotic arterioles, as well as to diapedesis from capillaries that apparently were overfilled because of retrograde passage of blood into the areas where the arterioles had become thrombosed. The glomeruli showed pictures similar to those described in the preceding cases, with the exception that in a great number the capillaries did not present collapsed tufts but well filled, even congested loops. In such instances, serial sections showed the vas afferens to be obliterated by a cellular proliferation in one part of its course (fig. 7). The atherosclerotic nature of this closure was suggested because the small vessel originated directly from a large interlobular artery with unquestionable atherosclerosis and in a place where a large atherosclerotic plaque was situated. Since no blood could pass through the arterioles, the congestion of the capillaries could have been the result only of retrograde passage of blood.

The pancreas and spleen showed advanced atherosclerosis, the pancreas to a severe, and the spleen to a moderate, extent arteriolar hyalinization.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; concentric hypertrophy of the left ventricle; dilatation of the right ventricle and auricle; atherosclerosis of the aorta and peripheral arteries; chronic emphysema of the lungs and anasarca.

CASE 7.—*History.*—M. S., a white woman, aged 54, single, was admitted to Mount Sinai Hospital on Aug. 13, 1928. The family history was irrelevant. At the age of 18, the patient was sent to Saranac Lake, N. Y., because she had bronchitis. Thirteen years before admission to the hospital, she was told that

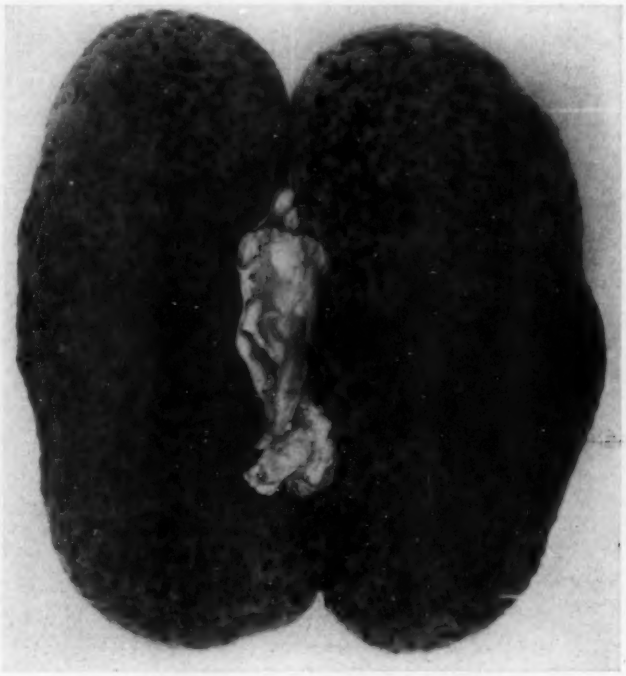

Fig. 6 (case 6).—Extensive hemorrhages on the surface.

nephrectomy was indicated, but it was not done. Five weeks prior to admission, she entered another hospital, where a diagnosis of chronic nephritis was made. Then for a few weeks she was in a convalescent home. Three days before admission, she became disoriented and delirious.

Examination.—The patient had a urinous odor of the breath. She was afebrile. She had occasional twitchings of the muscles of both upper and lower extremities. She had large hemorrhages in the skin of both legs. The fundi presented active neuroretinitis. The chest showed a flattening of the right upper side, dulness in the right upper lobes and a sinus just to the left of the ensiform cartilage, from which oozed greenish-white pus. Roentgen examination revealed tuberculous osteomyelitis of the second and seventh ribs. The heart was markedly enlarged. There were a bilateral Kernig sign, marked rigidity of the neck and a permanent

Babinski reflex in the toes. The spinal fluid was under pressure. The blood pressure was 165 systolic and 110 diastolic.

The urine contained albumin (++), many granular casts and white blood cells. The specific gravity was 1.020. The urea nitrogen of the blood was 43 mg. per hundred cubic centimeters.

Course.—The spinal fluid at the time of death contained 400 white blood cells, 80 per cent of which were polymorphonuclear leukocytes. Bacteriologic examination yielded negative results, and inoculation of a guinea-pig was unsuccessful because the animal died too early.

The clinical diagnosis was: tuberculous meningitis and chronic glomerulonephritis with azotemia.

The patient died two and one-half days after admission.

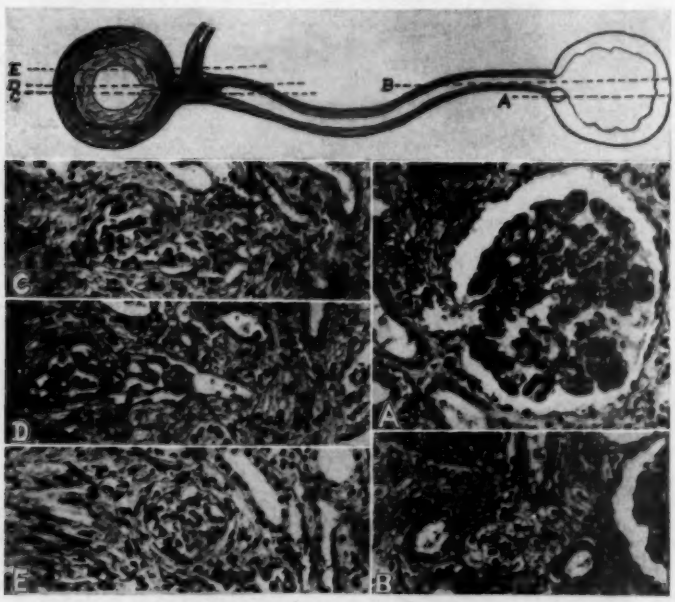

Fig. 7 (case 6).—A serial section reconstruction of a glomerulus and vas afferens: *A*, engorged capillaries and vas efferens; *B*, vas afferens (distal portion) patent; *C* and *D*, vas afferens (proximal portion where it branches off the interlobular artery) completely obliterated by cellular intimal proliferation, and *E*, cross-section of another obliterated arteriole. Note the reticulated arrangement of the cells.

Necropsy.—Necropsy was performed seven hours after the patient's death by Dr. Klemperer. Permission to open the head was not obtained. The right kidney weighed 120 Gm. and measured 10 by 5 by 3 cm. It had the same appearance as the kidneys in the other cases. The left kidney had a very narrow cortex due to compression caused by the tuberculous pyonephrosis.

Microscopically, the changes were almost identical with those in the other cases. The stroma increase was slighter. An extreme narrowing of the interlobular arteries leading to complete closure was observed with a proliferation of

the intima showing more fibrillar differentiation and distinct elastica lamellation within the outer zone.

Marked hyalinization of the arterioles was found in the spleen and pancreas; moderate hyalinization, in the liver and suprarenals.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; chronic tuberculous pyonephrosis of the left kidney with inspissation; concentric hypertrophy of the ventricle; hypertrophy and dilatation of the right ventricle; tuberculous osteomyelitis of the second right and seventh left rib, and multiple pleural adhesions.

CASE 8.—*History.*—L. R., a white man, 23 years of age, single, an embroiderer, was admitted to Mount Sinai Hospital on Feb. 16, 1926. The family history was irrelevant. The patient had scarlet fever at the age of 2; he had had no rheumatism or other acute infections. Tonsillectomy had been performed on him one year before because of frequent tonsillitis. For about five years he had had occasional severe bitemporal headaches, which gradually became worse. About one year before, he was told that he had high blood pressure. Eight weeks before, his vision became blurred. Two or three weeks before, he began to vomit; this condition had become worse within the last few days before admission. He had oliguria.

Examination.—On admission, the patient was drowsy and afebrile. His heart was enlarged to the left. On an average of four examinations, the blood pressure was 235 systolic and 150 diastolic. It fell to 168 systolic and 100 diastolic shortly before death. The fundi showed an advanced albuminuric retinitis. The urine decreased in amount.

Examination of the urine showed albumin +++; the sediment showed occasional red blood cells and many leukocytes. The urea nitrogen of the blood was 63 mg.; the creatinine, 8 mg., and the uric acid, 11 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed: hemoglobin, 70 per cent; red blood cells, 3,340,000, and white blood cells, 17,000, with polymorphonuclear leukocytes 83 per cent, lymphocytes 15 per cent, and mononuclear cells, 2 per cent.

Course.—The patient became comatose forty-eight hours before death and died on February 24, eight days after admission.

Necropsy.—Necropsy was performed eighteen hours later by Dr. Gross. The left kidney weighed 105 Gm., and the right, 120 Gm. Each measured 11 by 5 by 3 cm. The surfaces were slightly granular. Many hemorrhages were seen.

Microscopic examination showed insignificant, only focal increase in the stroma. Occasional small anemic infarcts were seen, with leukocytic infiltrations. There was marked dilatation of the convoluted tubules, which contained occasional polymorphonuclear leukocytes. Only a few fibrosed glomeruli were observed. The majority were bloodless, with collapsed capillaries; some, however, were engorged, almost infarcted. They presented slight proliferative and degenerative epithelial changes. There was marked necrosis of arterioles, with hemorrhagic penetration of the wall and often thrombotic occlusion. The vasa afferentia were focally extremely narrow; in some parts of the cortex, however, they were not altered. The interlobular arteries were extremely narrowed by cellular intimal proliferation.

The arterioles of the spleen, pancreas and suprarenals showed hyalinization.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; acute fibrinous pericarditis, and hemorrhagic focal pneumonia of the left lung.

CASE 9.—*History.*—H. P., a white woman, 26 years of age, married, a housewife, was admitted to Mount Sinai Hospital on Nov. 7, 1925. The father died of kidney trouble. The patient had measles in childhood. Seven years before admission, she had typhoid fever. Two years before, a tonsillectomy was performed on her. Occasionally she had severe headaches. For one and one-half years, the headaches had become worse and more frequent, which prevented her from working. For one year, she had had attacks of substernal pain, and for seven months, nocturia. For two weeks, she had suffered from uncontrollable vomiting. Within the last thirty-five hours before admission she was anuretic.

Examination.—When admitted, she was afebrile and restless, tossing about and complaining of extreme weakness. The breath was uriniferous. The heart was markedly enlarged. The blood pressure in an average of eleven readings was 230 systolic and 145 diastolic. The fundi showed neuroretinitis. Very small amounts of urine were passed. Concentration was from 1.006 to 1.012. The result of the test for albumin was ++. The sediment contained a few granular casts, white blood cells and an occasional red blood cell. The blood showed: urea nitrogen, from 81 to 102 mg.; uric acid, 8.5 mg., and creatinine, 14 mg., per hundred cubic centimeters. The blood count gave: hemoglobin, 60 per cent; red blood cells, 3,320,000, and white blood cells, 8,200.

Course.—Fluids were forced, which caused a drop in the urea nitrogen of the blood, but edema and ascites developed. The patient died of uremia on November 19, twelve days after admission.

Necropsy.—On the day after death, Dr. Romanoff made a postmortem examination. The right kidney weighed 120 Gm. and measured 11 by 6 by 3 cm. The left weighed 40 Gm. and showed only three pyramids. They showed slightly granular surfaces and many hemorrhages.

Microscopically, the kidneys presented a diffuse increase in the stroma and many hemorrhages. The same glomerular changes were seen as in the other cases. There was severe arteriolar necrosis without a perivascular inflammatory reaction. Portions of the interlobular arteries were markedly narrowed by dense intimal proliferation.

The arterioles of the spleen and pancreas showed hyalinization.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; acute fibrinous pericarditis, and hypoplasia of the left kidney, with anomalous implantation of the ureter.

CASE 10.—*History.*—T. P., a colored woman, 57 years of age, married, a housewife, was admitted to the hospital on July 19, 1927. The patient's family history was irrelevant. Nine years before she had influenza. Six children were living and well; one child had died. The menopause occurred five years before. The patient had never been sick. Three weeks before, she became ill with general malaise, vomiting and incontinence. Then she became restless, and she said that she felt a lump behind the sternum. She became disoriented and psychotic.

Examination.—She was admitted to the hospital in stupor, but could be aroused with difficulty. The temperature was normal. The heart was slightly enlarged. The blood pressure was 165 systolic and 110 diastolic. The fundi showed albuminuric retinitis and optic neuritis.

Only 30 cc. of urine was passed in the previous twenty-four hours. The concentration was 1.005. Albumin was ++; the sediment contained many granular and hyaline casts and white blood cells. The blood showed 186 mg. of urea nitrogen per hundred cubic centimeters. The Wassermann reaction was negative.

Course.—The patient died on July 20, twenty-four hours after admission.

Necropsy.—Necropsy by Dr. Klemperer, fifteen hours later, showed the kidneys to be smaller than normal (weight omitted), measuring 9 by 5 by 2 cm., with diffuse slightly elevated granulations and numerous hemorrhages.

Microscopic examination revealed: a diffuse increase in stroma, with atrophy of the tubules; small glomeruli, often bloodless, with collapsed capillaries; few hyalinized glomeruli; occasional malpighian corpuscles with hemorrhagic infarction and necrosis of the tufts; frequent arteriolonecrosis without perivascular inflammation, and marked narrowing of the interlobular arteries by a dense, fibrillar connective tissue, with coarse elastica lamellation in the outer zone and occasional fine elastic fibers in the inner layer.

The arterioles of the liver, spleen and pancreas showed moderate hyalinization.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; cerebral atherosclerosis; small acute ulcer of the stomach; hypertrophy of the left ventricle, and a small endothelioma of the dura.

CASE 11.—*History.*—T. L., a white woman, aged 46, married, a housewife, was admitted to the hospital on Sept. 5, 1928. The patient's father died at the age of 72; the mother died as a young woman, the cause of death being unknown. One sister had kidney trouble. The patient gave no history of having had scarlet fever, rheumatic fever or diphtheria. Nineteen years before, she had an abscess of the breast. She had occasional colds. Six children were living and well; there had been three miscarriages. For three years the patient had suffered from severe suboccipital headaches in the morning. For three years she had had nocturia, also frequency of urination during the day. There was occasional incontinence at night. She noted precordial pressure and palpitation. All symptoms grew worse, especially during the three weeks before admission.

Examination.—When admitted, the patient complained of severe precordial constriction; a few minutes later she had a severe attack of dyspnea and a sensation of impending death. She was afebrile. Her breath was uriniferous. There was enlargement of the heart. The blood pressure, in an average of seven readings, was 210 systolic and 135 diastolic. The fundi showed acute neuroretinitis on an old atherosclerotic basis.

The urine was small in amount; the albumin was ++; the sediment contained many white blood cells, a few red blood cells and rare granular casts; the concentration was from 1.010 to 1.012; the phenolsulphonphthalein excretion was 0 after four hours. The blood showed: urea nitrogen, from 93 to 108 mg.; uric acid, 5.1 mg., and creatinine, from 9.7 to 12.4 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The hemoglobin was 74 per cent at admission; it fell to 46 per cent before death. The red blood cells numbered 4,600,000; the white blood cells, 11,400.

Course.—Pulmonary edema and cardiac failure developed, and the patient died on September 28, three weeks after admission.

Necropsy.—Two hours later, Dr. Otani made a postmortem examination. The kidneys weighed 85 Gm. each; their size was 10 by 5 by 3.5 cm. They showed diffuse prominent grayish-yellow granulation and a few punctate hemorrhages. There was marked atherosclerosis of the renal artery (fig. 8).

Microscopic examination revealed a diffuse marked increase in the stroma, with separated islands of normal tubular parenchyma. The glomeruli were not extensively fibrosed, but were mostly small and anemic, with collapsed capillaries (fig. 9). There was moderate arteriolonecrosis, but severe intimal proliferation of the interlobular arteries with excessive narrowing of the lumen. There was

elastica lamellation in the outer layer and cellular proliferation of connective tissue in the inner layer, which showed fatty infiltration and focal necrobiosis, with impregnation of the wall by erythrocytes (fig. 10 *A*).

The spleen was very firm. The surface was nodular. The large nodes were separated by firm, depressed, scarlike areas. On section, the pulp was purplish red. The trabeculae were prominent. Several irregular, firm and dry yellowish-white areas of necrosis interrupted the otherwise dark red cut surface, giving the spleen a mosaic-like appearance.

Microscopic examination showed within the deeply congested pulp several necrotic areas of irregular outline. The intratrabecular arteries and their branches showed extreme narrowing due to a cellular intimal proliferation in the outer

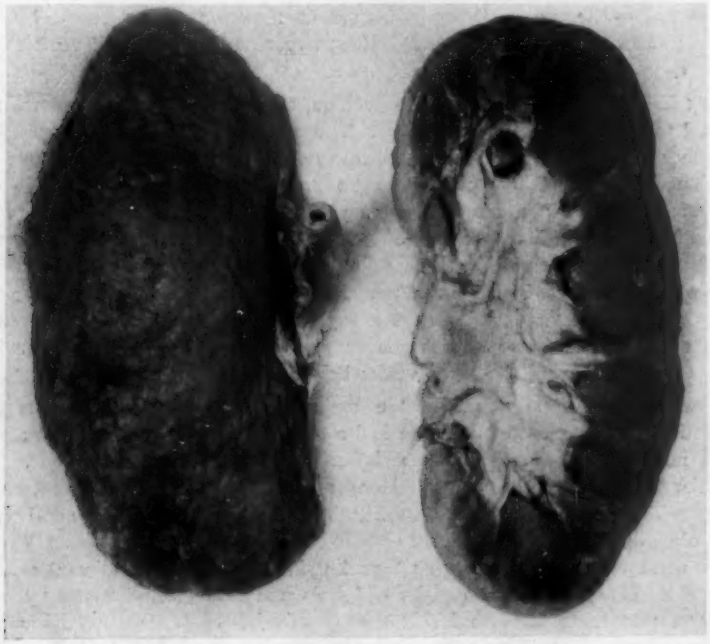

Fig. 8 (case 11).—The more advanced type of renal atrophy with prominent granulation. Note the few hemorrhages on the surface, the narrow cortex on cross-section and the severe atherosclerosis of renal artery.

coat of which there was distinct coarse elastica lamellation (fig. 10 *B*). The narrow lumen was occasionally obliterated by hyaline thrombi.

The pancreatic arteries of the same size as the interlobular renal arteries showed extreme narrowing due to the same cellular intimal proliferation (fig. 10 *C* and *D*).

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy and dilatation of both ventricles and auricles; chronic passive congestion of the lungs, liver and spleen; brown induration of the lungs; generalized atherosclerosis; hydrothorax; ascites, and multiple necrosis of the spleen.

Case 12.—*History.*—T. S., a white woman, aged 55, a housewife, was admitted to the hospital on Oct. 1, 1927. The family history was irrelevant. The previous

history was unimportant. The menopause occurred when she was 45 years old. About twenty years before admission to the hospital, the patient was told that she had hypertension. For ten years she had had increasing dyspnea on moderate exertion. Slight nocturia had developed in the past five years. She was admitted to the hospital because of hypertension and persistent vomiting for weeks.

Examination.—The patient was lethargic and afebrile and had a urinous breath. The heart was markedly enlarged. The fundi showed neuroretinitis. The blood pressure was 234 systolic and 110 diastolic.

The amounts of urine were small. The albumin was ++; the sediment contained a few coarse granular casts and many white and red blood cells. The

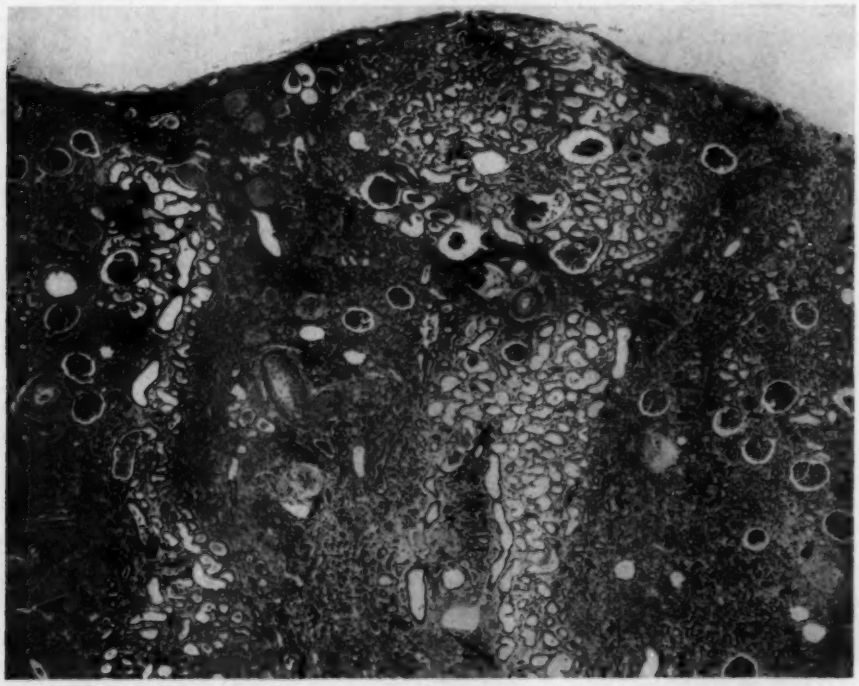

Fig. 9 (case 11).—The advanced increase in the stroma and the atrophy of the parenchyma. Compare this with figure 4.

concentration was from 1.007 to 1.010. The blood disclosed urea nitrogen, 121 mg.; uric acid, 5.4 mg., and cholesterol, 218 mg., per hundred cubic centimeters. The Wassermann reaction was negative. The blood count gave: hemoglobin, 70 per cent, and white blood cells, 11,200, with polymorphonuclear leukocytes, 84 per cent, and lymphocytes, 16 per cent.

Course.—The patient became stuporous. Muscular twitchings developed. Death occurred on Oct. 7, 1927, six days after admission.

Necropsy.—Five hours later, Dr. Otani made a postmortem examination. The left kidney weighed 110 Gm.; the right, 120 Gm. The surfaces were finely granular throughout. The cortex was narrow; the cortical markings were obscured by a grayish-white infiltration.

Microscopic examination revealed diffuse marked increase in the stroma, but many islands of dilated, otherwise normal tubules. The tubules elsewhere were separated and often atrophic. The glomeruli were not extensively fibrosed, but were generally anemic or bloodless, except for a few that showed hemorrhagic infarction. Occasional epithelial proliferation was seen. Necrosis of the tufts was rare. Arteriolonecrosis without perivascular infiltration was present. There was excessive narrowing of interlobular arteries, with distinct elastica lamellation in the outer coats of the intima.

The arterioles of the pancreas, liver, spleen and suprarenals showed marked hyalinization of the arterioles and atherosclerotic narrowing of the small arteries.

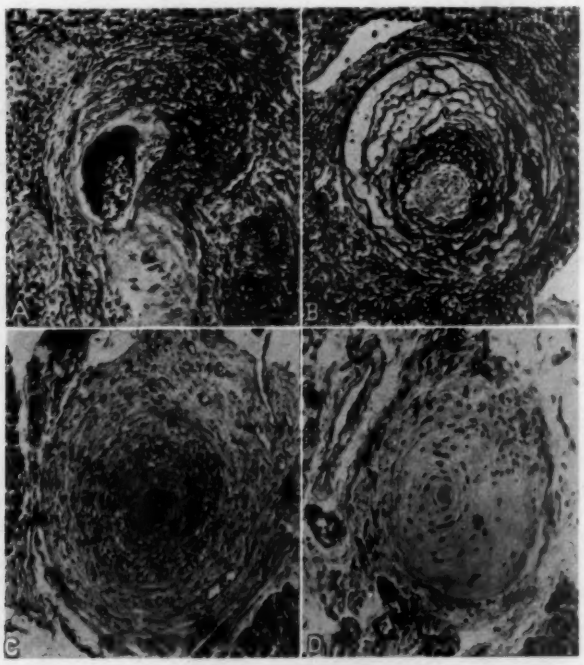

Fig. 10 (case 11).—*A*, an interlobular artery of the kidney showing intimal proliferation and focal necrobiosis and aneurysmic dilatation. The wall and the perivascular stroma are impregnated with erythrocytes and hemoglobin droplets. *B*, splenic artery of the same caliber as that shown in *A* found near necrosis, showing closure of lumen by a similar intimal proliferation. Note the conspicuous elastica lamellation and the numerous foam cells as evidence of the degenerative nature of the process. *C* and *D*, identical arterial changes in the pancreas. Note the hemorrhagic impregnation of the wall in *C*.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; atherosclerosis of the aorta, coronary arteries and pulmonary artery; chronic passive congestion of the liver, lungs and spleen; ascites, and calcified tuberculosis of the left lung and tracheobronchial lymph nodes.

Case 13.—*History.*—H. O'N., a colored man, married, aged 53, a waiter, was admitted to the hospital on Jan. 16, 1929. The family history was irrelevant.

The patient was a user of alcohol. Twelve years before, the patient had rheumatism. Two and one-half months before, a stone in the bladder was removed by crushing. For two and one-half months, the patient had suffered from frontal headaches in the morning. Two weeks before admission, he suddenly became seriously sick, began to vomit and became drowsy and lethargic.

Examination.—When admitted, he was afebrile and cachectic and had a urinous odor to his breath. He showed occasional muscular twitchings. The heart was enlarged. The fundi showed neuroretinitis, atherosclerosis and atrophy of the optic nerve. The blood pressure was 180 systolic and 100 diastolic.

The output of urine was smaller than the intake of fluid. The concentration was 1.010; the result of the test for albumin was ++; the sediment contained a few white and red blood cells. The blood showed: urea nitrogen, 190 mg.; uric acid, 15 mg., and creatinine, 16 mg., per hundred cubic centimeters. The Wassermann reaction was ++++. The blood count showed: hemoglobin, 39 per cent, and white blood cells, 15,200, with polymorphonuclear leukocytes, 84 per cent, lymphocytes, 14 per cent, and mononuclears, 2 per cent.

Course.—The patient died on January 18, two days after admission. Urea crystals had developed on his face and neck.

Necropsy.—Two hours later, Dr. Klemperer performed an autopsy. The right kidney weighed 95 Gm.; the left, 140 Gm. Both showed diffuse flat granulations. The right kidney showed a deep scar penetrating the cortex in its middle third, apparently a circumbscribed atrophy caused by a calculus. Numerous hemorrhages were evident on the surface and section and within the pelvis.

Microscopic examination showed a moderate but diffuse increase in the stroma, with separation and frequent atrophy of the tubules. Only a few hyalinized glomeruli were seen; generally they were small and anemic and occasionally they showed epithelial proliferation, fatty and hyaline droplet degeneration and necrosis of loops. Arteriolonecrosis was present, but was not severe. There were no perivascular infiltrations. Excessive narrowing of the interlobular arteries by a cellular intimal proliferation was seen. Elastica lamellation was present in the larger branches.

The arterioles of the spleen, liver, pancreas and stomach showed marked hyalinization. Within the intestines, only moderate arteriolosclerosis was seen. The small arteries showed moderate atherosclerosis, except in the pancreas, where arteries of the caliber of the interlobular renal arteries were found with extreme cellular intimal thickening. In their vicinity, small areas of necrosis of the parenchyma were encountered.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy and dilatation of the left ventricle; atherosclerosis of the aorta and peripheral blood vessels; uremic ulcers of the large intestine, and circumscribed cicatricial atrophy of the right kidney (stone).

CASE 14.—*History.*—M. B., a white woman, 39 years of age, married, a telephone operator, was admitted to the hospital on March 26, 1929. The family history was irrelevant. In childhood, the patient had diphtheria, scarlet fever and measles. At the age of 18 years, she had a left mastoidectomy. She had suffered two miscarriages. She had had an appendectomy and an oophorectomy. During the last year, she had lost 80 pounds (36.3 Kg.). Four months before admission, she was hit on the eye by a baseball. She went to the neurologic institute because of nervousness and defective vision. She was admitted to Mount Sinai Hospital because of sudden loss of speech and difficulty in swallowing.

Examination.—When admitted, she was afebrile and aphasic, with a partial motor aphasia and right central facial paresis. The deep reflexes on the left side were exaggerated. Babinski's sign was noted on the left side. The clinical diagnosis was: focal cerebral lesions of the left hemisphere. The fundi showed neuroretinitis. The heart was enlarged. The blood pressure was between 185 systolic and 90 diastolic and 240 systolic and 150 diastolic.

Examination of the urine showed: concentration, 1.010; albumin, +++, and a few red and white blood cells in the sediment. The blood showed: urea nitrogen, from 45 to 57 mg.; uric acid, 8 mg., and creatinine, 6.2 mg., per hundred cubic centimeters. The blood count gave: hemoglobin, 35 per cent; red blood cells, 1,250,000, and white blood cells, 11,800, with polymorphonuclear leukocytes, 86 per cent.

Course.—The patient began to have difficulty in respiration and later pericarditis, and died on April 8, twelve days after admission.

Necropsy.—Eight hours later, a postmortem examination was made by Dr. Otani. Permission to examine the brain was not obtained. The kidneys weighed 120 and 110 Gm. They showed diffuse flat granulations and numerous hemorrhages. There was severe atherosclerosis of the renal artery.

Microscopic examination revealed a diffuse increase in the stroma but not extensive scar formation. The structure of the cortex was not completely obscured. The tubules were separated and often atrophic. Few fibrosed glomeruli were encountered. Many glomeruli were small and anemic, with collapsed tufts. Some showed partial hyalinization. Occasional epithelial proliferation and fatty hyaline droplet degeneration of the proliferated and desquamated cells were seen. Occasional necrosis of the capillaries was seen. Arteriolonecrosis without perivascular infiltration and extreme intimal proliferation of the interlobular arteries were features.

The arterioles of the spleen, suprarenals and pancreas showed severe hyalinization, which was less marked in the liver, intestine and esophagus. There was severe atherosclerosis of branches of the coronary arteries.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the left ventricle; atherosclerosis of the aorta and coronary arteries; acute fibrinous pericarditis; bronchopneumonia of the right lower lobe; fatty degeneration and fibrosis of the myocardium, and multiple calculi of the pancreatic duct, with fibrosis of the body.

Case 15.—*History.*—S. G., a white man, aged 36, a laborer, was admitted to the hospital on Aug. 9, 1929. The family history was irrelevant. The previous history was unimportant. Two years before admission, the patient had frontal headaches and occasional epistaxis. He was informed that he had high blood pressure. He stopped work and improved under rest. Three months before, the frontal headaches reappeared. He had nocturia (three or four times). Palpitation and precordial pains were experienced on exertion. Dimness of vision had been present for four weeks. For three days there had been nausea and vomiting.

Examination.—Physical examination showed a very sick anemic person with a urinous odor of the breath and no elevation of temperature. He was dyspneic and orthopneic at rest. The heart was markedly enlarged. The fundi disclosed hypertensive neuroretinitis. The blood pressure, in an average of four readings, was 234 systolic and 143 diastolic.

The urine showed a concentration of from 1.006 to 1.010. There was from a trace to + albumin. The sediment contained casts and white blood cells but no red blood cells. The blood showed: urea nitrogen, from 79 to 135 mg., uric acid,

8.5 mg., and creatinine, 10 mg., per hundred centimeters. The blood count gave: hemoglobin, from 42 to 23 per cent; white blood cells, 7,600, and red blood cells, 2,200,000.

Course.—The patient went continuously down hill, and died of uremia on August 30, three weeks after admission.

Necropsy.—Nineteen hours after death, a postmortem examination was made by Dr. Otani.

The weight of the left kidney was 100 Gm.; that of the right, 80 Gm. There were several depressed scars, which had destroyed the entire cortex, and a diffuse flat granulation of the entire surface. The cortical markings were indistinct.

Microscopic examination showed the cortical structure obliterated in many fields by scar tissue within which numerous fibrosed glomeruli were seen. Outside of these areas, however, there was not a marked increase in the stroma. Here the glomeruli were frequently markedly congested, but others were small and collapsed. Arteriolonecrosis was found rarely. The interlobular and arcuate arteries, however, showed an extreme degree of narrowing due to a combination of typical atherosclerosis with elastica lamellation in the outer, and a cellular intimal proliferation in the inner, coats.

Only the arterioles of the liver and spleen showed moderate hyalinization.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of the heart, especially of the left ventricle; acute fibrinous pericarditis; atherosclerosis of the aorta and of the pulmonary and coronary arteries; acute enterocolitis; focal pneumonia of the right lower lobe; bilateral hydrothorax; ascites and passive congestion of the liver and spleen.

CASE 16.—*History.*—E. L., a white woman, aged 32, single, a dressmaker, was admitted to the hospital on May 28, 1929. The family history was irrelevant. The patient had always been well, except for influenza in 1918. Two years before, she was refused life insurance because of high blood pressure. She felt, however, perfectly well at that time. One year before, she noticed an increasing weakness and easily became fatigued. Six months before her blood pressure was 280. She began to have frequency of urination and developed edema of the ankles and a swelling in the sacral region. Two weeks before admission, she had an attack of complete amaurosis, which disappeared. She was admitted to the hospital because of increasing dyspnea and orthopnea.

Examination.—On admission, she was afebrile, but very sick, with a urinous odor of the breath. The heart was enlarged. The fundi showed hemorrhagic neuroretinitis. There was marked edema of the lower extremities. The abdomen was distended, and the liver was enlarged. Scattered about the abdomen were small purpuric hemorrhages. The blood pressure was 242 systolic and 112 diastolic.

The urine showed a specific gravity of from 1.004 to 1.012; albumin, +. The sediment contained white and red blood cells. The blood yielded urea nitrogen, from 87 to 183 mg.; uric acid, 14 mg., and creatinine, 16 mg., per hundred cubic centimeters. The blood count gave: hemoglobin, 39 per cent; white blood cells, 7,400, and polymorphonuclear leukocytes, 86 per cent. The Wassermann reaction was negative.

Course.—The patient became increasingly drowsy. Urea crystals developed on her face. She had numerous twitchings of the extremities and hiccup. She died on June 2, eleven days after admission.

Necropsy.—The following day, necropsy was performed by Dr. Otani. The kidneys weighed 85 Gm. each. The surfaces were diffusely granular; the granules

were larger than in the other cases. On the surface and on cross-section there were numerous hemorrhages.

Microscopic examination showed a diffuse increase in the stroma, with numerous connective tissue scars alternating with islands of well preserved tubules. The cortical structure was obscured by the presence of many atrophic and dilated tubules. Glomerular fibrosis was more conspicuous on the surface than inside the cortex, but was not extensive. Various phases of the process of atrophy were present. The majority of the malpighian corpuscles were not hyalinized, but were small and anemic, with collapsed, often thickened, capillary loops. Rarely there were necrosis of the tufts and epithelial proliferation. Arteriolar hyalinization was conspicuous. A few necrotic arterioles were seen, without perivascular cell infiltration. There was extreme narrowing of the interlobular arteries by dense intimal proliferation with conspicuous elastica lamellation in the outer zone. However, here and there one found a more cellular intimal proliferation.

Within the body of the pancreas, an area 1.5 cm. in diameter was necrotic and liquefied. A few smaller necrotic foci were also present.

Microscopically, numerous foci of necrosis of the parenchyma were observed, some with organization and some with advanced fibrosis. The arteries of the size of the arcuate arteries of the kidneys and their interlobular ramifications showed an extreme cellular intimal thickening, which often almost occluded the lumen. Occasionally, the lumen was filled with a thrombus, which sometimes showed organization and canalization. The internal elastic lamella sharply separated the media from the intima. The fibroblasts that formed the thickened intima often showed hyaline droplet degeneration and necrobiosis. The walls of such vessels were often impregnated with red blood cells. An inflammatory reaction was seen only in the adventitia and media of vessels lying within or next to necrotic foci. Only one arteriolar cross-section showed necrosis without perivascular infiltration.

Routine examination of the other organs revealed only within the spleen advanced atherosclerosis of the small arteries and hyalinization of the arterioles. The liver and the gallbladder showed only slight changes. The coronary arteries were severely affected by atherosclerosis, but the myocardial branches showed no changes.

Diagnosis.—The diagnosis was: malignant nephrosclerosis; hypertrophy of both ventricles of the heart; atherosclerosis of the aorta and of the coronary and splenic arteries; focal necrosis of the pancreas; pseudomembranous enteritis (ileum and jejunum); purulent bronchitis and peribronchitis; chronic calcified tuberculosis of both lungs and tracheobronchial lymph nodes; hydrothorax on the right side, and ascites.

SUMMARY OF CASES

Before entering on a detailed discussion and evaluation of our observations, it may be well to summarize the clinical events and the morbid process.

The importance of these cases for clinical medicine and pathology is obvious from table 1, which presents the number and percentage of deaths from the different types of renal disease observed by us within the last three years.

In this survey, almost 30 per cent of all deaths from renal insufficiency were of the type of malignant nephrosclerosis as understood by Fahr. The ages of the patients are tabulated in table 2.

The average age in our cases was 39 years. In agreement with Fahr and other authors, we found that the majority of cases occurred in persons below 50 years; and this is contrasted with the situation in cases of benign sclerosis, in which the majority of the patients were above 50 years.

Cases occurred equally in both sexes. We observed cases in eight females and eight males. The average age of the female patients was 44 years, and that of the male patients was 30 years.

Except in one case, fatal renal insufficiency was preceded by a pure hypertensive phase with symptoms of varying degree. The duration

TABLE 1.—*The Number and Percentage of Deaths from Different Types of Renal Insufficiency Observed by the Authors*

	Number of Deaths	Percentage
Acute and subacute glomerular nephritis	8	13.8
Chronic glomerular nephritis	19	32.7
Malignant nephrosclerosis	16 (1)*	29.3
Benign decompensated nephrosclerosis (Fahr)	7	12.0
Amyloid contracted kidney	4	7.0
Polycystic kidney	3	5.2
Total	58	100.0

* See case 18.

TABLE 2.—*Age of Patients with Malignant or Benign Sclerosis*

Age	Malignant Sclerosis		Benign Sclerosis	
0 to 10	1		0	
11 to 20	0		0	
21 to 30	4	75%	0	29%
31 to 40	3		4	
41 to 50	4		14	
51 to 60	4		16	
61 to 70	0	25%	22	71%
71 to 80	0		6	
Total	16		62	

of the antecedent hypertension was not easy to determine. In several cases, the hypertension had been discovered accidentally in an examination for life insurance, with the patient apparently in perfect health. In other cases, symptoms had set in so insidiously that it was impossible to say precisely when they had appeared. This antecedent phase did not differ in any way from other hypertensive states. It passed into the terminal uremic stage abruptly or sometimes after an interval of several months with increased intensity of hypertensive symptoms, such as uncontrollable headaches or occasional cardiac insufficiency, or after a period of failing vision. The exact start of the renal insufficiency was ascertained only when the patients had been under careful medical control for some time before their admission to the hospital; otherwise, it could be only surmised from the clinical symptoms of obstinate nausea

and vomiting, restlessness and psychic disturbance. The temperature was always normal on admission. The chemical examination of the blood, performed in every case immediately after admission, always disclosed a marked increase in the values of urea nitrogen, uric acid and creatinine. The systolic and diastolic blood pressure was much elevated, as a rule, the average being 232 systolic and 140 diastolic. In eight cases, during the last days of illness, there were oliguria and even anuria. The specific gravity of the urine was always low, and the concentrating power of the kidneys was lost. Albumin was present regularly; the sediment contained hyaline and granular casts, white blood cells and occasionally blood. Examination of the blood often showed considerable anemia, but leukocytosis only occasionally. The Wassermann reaction was negative, except in one case. In all the other cases, there was neither clinically nor anamnestically any evidence of previous syphilitic infection. The eyegrounds in all cases, except one in which they were not examined, revealed neuroretinitis. The average duration of the renal insufficiency, so far as it could be determined from the history, was thirty-two days. Especially striking was the rapid course of the illness, which went on without remission and could not be influenced by therapy once the uremic symptoms had appeared.

The gross anatomic picture was characterized by predominant changes in the kidneys and the heart. In thirteen cases there was atherosclerosis of the aorta and peripheral blood vessels. (Unfortunately, permission to examine the brain was secured in three cases only). Acute fibrinous pericarditis occurred in six cases. Circumscribed anemic necrosis of the pancreas due to severe alteration of the small vessels was observed twice, and once multiple necrosis of the spleen was found. Hemorrhagic enterocolitis with or without ulcerations was present in four cases. Purpuric skin eruptions were encountered in two cases, and urea crystals in two cases. Terminal bronchopneumonia was observed seven times. Hydrothorax, ascites or anasarca existed in five cases. Chronic tuberculous lesions of the lungs were found in four instances. An old tuberculous pyonephrosis was present in one case in which there also existed a tuberculous osteomyelitis of the sternum and two ribs.

The heart was markedly enlarged in every case, except in one in which there was extreme emaciation of the body. The average weight of the heart, including the aorta ascendens, was 550 Gm. The left ventricle was always preponderant, but coexisting hypertrophy of the right ventricle was seen in six cases, in two of which there was gross brown induration of the lungs, indicating relative insufficiency of the left side of the heart. Sclerosis of the coronary arteries, moderate in degree, was present in ten cases. One case showed an old thrombotic

occlusion of the ramus posterior descendens of the right coronary vessel and another severe atherosclerosis of the same branch; in both cases there was advanced myocardial fibrosis.

The kidneys in the majority of instances were only slightly reduced in size, the average weight being 113 Gm. In one instance, the left kidney was hypoplastic, weighing 40 Gm., and showing only three pyramids. The renal surface was always diffusely granular with flat irregularly sized brown elevations above slightly depressed red areas. A few deeper depressions of the type found in renal atherosclerosis of the decrescent form were observed in eight cases. These diffuse depressed areas gave the organ the predominant brownish-red color which contrasted with the bright petechial hemorrhages, more or less numerous, seen in every case. In one case, the surface and the cross-section were densely sprinkled with hemorrhages, ill-defined in outline, and of the size of a pinhead or larger. On cross-section, the cortex and the medulla were for the most part sharply demarcated; the cortical markings, however, were obscured by infiltrating grayish streaks and flecks. The cross-sections of the arcuate vessels were for the most part thickened and gaping. The medulla was generally normal. The pelvis frequently showed deep red hemorrhages. The renal artery was markedly thickened in six cases.

The microscopic changes disclosed a uniformity similar to that noted in the gross lesions. Chief among these changes was the severe vascular damage. The extreme narrowing of the interlobular arteries caused by a cellular intimal proliferation, and the necrosis of the arterioles, were present in every instance. The alteration of the glomeruli, though less conspicuous, consisted in (1) collapse of the capillaries and anemia; (2) degenerative changes of the capillary wall and its epithelial lining, varying in degree from fatty infiltration and hyaline droplet degeneration to complete necrosis, and (3) epithelial proliferation and occasional leukocytic accumulation. The acute alteration of the tubular parenchyma evidenced by fatty infiltration, hyaline degeneration and necrosis was never lacking. In several instances, smaller and larger areas of infarction with anemic necrosis took place. Atrophy of the convoluted tubules varied in intensity corresponding to the degree of stroma proliferation. This was never limited to the surface of the cortex, but involved equally the entire cortical zone.

Routine examination of the other organs showed that the small arteries of the spleen were severely atherosclerotic and narrowed in six cases, those of the pancreas in four cases. With these organs omitted, similar changes were seen but seven times in all the viscera in all the cases. The arterioles of the pancreas were hyalinized and narrowed ten times; once arteriolonecrosis was found. Those of the spleen were

similarly involved only five times. In all the other organs in all the cases, marked arteriolosclerosis was found but five times. A cellular intimal thickening similar to that in the kidneys occurred in only four cases. Involvement of the choroid, however, was revealed in every case examined. These choroid changes consisted not only in this cellular intimal proliferation but in severe arteriolohyalinization in every case and actual arteriolar necrosis in one instance.

The tabulation of changes noted by us as existing in the small vessels elsewhere than in the kidneys is in accord with similar observations of other authors in connection with hypertensive states (Fahr,[20] Herxheimer,[27] Fishberg [28]). Just as they found that arteriolosclerosis affected the vessels of the pancreas and the spleen most frequently after those of the kidneys, so, too, we observed a similar relationship and frequency in these organs with regard to the described changes in the small vessels. It must be emphasized that the involvement of the small and smallest arteries was never general.

Multiple necrosis of the spleen due to degenerative vascular obliteration was first reported by Feitis [29] in two cases of chronic interstitial nephritis associated with uremia. Lubarsch [30] and Hosoi [31] published identical observations; in their cases there existed also a vascular renal disease. Similar lesions in the pancreas have been recorded in only a few instances (Roessle,[32] Engel [33]).

COMMENT

It is evident that our observations conform with those in a group of cases that were first reported by Volhard and Fahr as "Kombinations Form." Within recent years, the term "malignant nephrosclerosis" has been generally accepted in the German literature. In the American literature, Bell and Clawson [34] briefly referred to nine cases of the same type, terming them "chronic hypertension with acute uremia,"

27. Herxheimer, G.: Zur Frage der Arteriolosklerose, Centralbl. f. allg. Path. u. path. Anat. **33**:111, 1923.

28. Fishberg, A. M.: Anatomic Findings in Essential Hypertension, Arch. Int. Med. **35**:650, 1925.

29. Feitis, H.: Ueber multiple Nekrosen in der Milz, Beitr. z. path. Anat. u. allg. Path. **68**:297, 1921.

30. Lubarsch, O., in Henke and Lubarsch (footnote 20, 1927, vol. 1, p. 448).

31. Hosoi, K.: Multiple Necrosis of the Spleen, Arch. Path. **6**:26, 1928.

32. Roessle, R.: Beiträge zur Kenntnis der gesunden und der kranken Bauchspeicheldrüse, Beitr. z. path. Anat. u. z. allg. Path. **69**:163, 1921.

33. Engel, T.: Zur Pathologie der Fettgewebs und Pankreasnekrose, Inaug. Diss., Frankfurt am Main, 1921; cited from Henke and Lubarsch (footnote 20, 1929, vol. 5, p. 307).

34. Bell, A. T., and Clawson, B. J.: Primary (Essential) Hypertension, Arch. Path. **5**:939, 1928.

while Fishberg [35] for such cases employs the term "malignant phase of essential hypertension" (see also Sternberg [36]). The term "malignant hypertension" was used by Keith and Wagner [37] to designate a morbid condition characterized by progressive severe hypertension and neuroretinitis. This term may properly be applied to our cases also, particularly in their clinical course before signs of renal insufficiency intervened. However, as renal insufficiency developed in our cases, it is suggestive that they represent the terminal phase of malignant hyper-

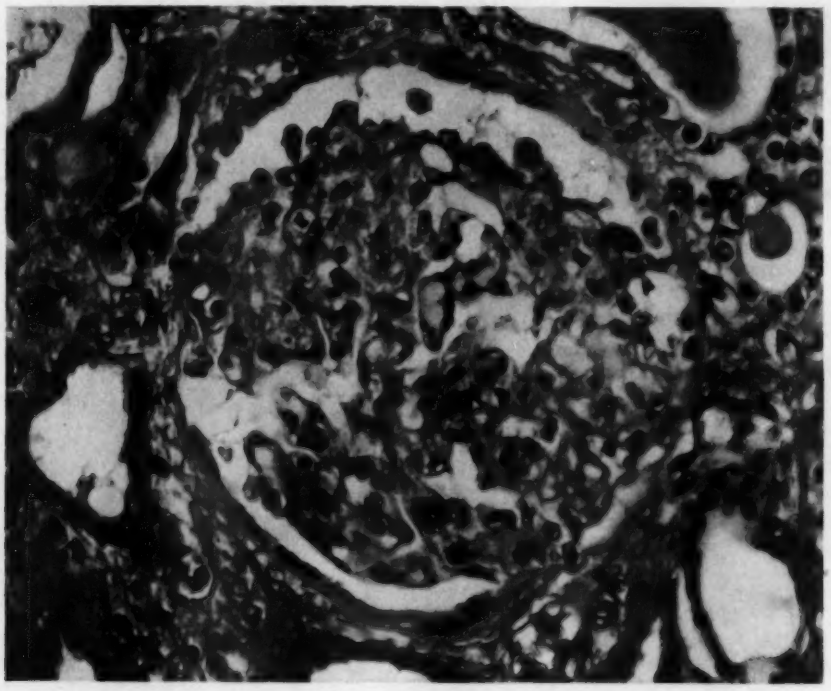

Fig. 11 (case 1).—Glomerulus showing fusion of capillary loops, epithelial desquamation, fatty infiltration (foam cells) and thickening of basement membranes.

tension. This point of view is supported by the fact that Keith, Wagener and Kernohan,[38] too, came on renal insufficiency in a number of their cases.

35. Fishberg, A. M.: Hypertension and Nephritis, Philadelphia, Lea & Febiger, 1930.

36. Sternberg, B.: Thrombo-Angionecrotic Changes of the Kidneys in Chronic Nephritis, Arch. Int. Med. **44**:272, 1929.

37. Wagener, M. P., and Keith, N. M.: Cases of Marked Hypertension, Adequate Renal Function and Neuroretinitis, Arch. Int. Med. **34**:374, 1924.

38. Keith, N. M.; Wagener, H. P., and Kernohan, J. W.: The Syndrome of Malignant Hypertension, Arch. Int. Med. **41**:141, 1928.

The microscopic features that permit a differentiation of these cases from other vascular, or from inflammatory renal, diseases are: (1) arteriolonecrosis and extreme cellular intimal thickening of the larger interlobular and so-called arcuate arteries, and (2) degenerative, proliferative and slight exudative focal glomerular lesions. The question arises as to the relative importance of these alterations and their correct pathogenic interpretation.

Focal glomerular alterations characterized by fusion and necrosis of capillary loops, endothelial swelling and epithelial proliferation and

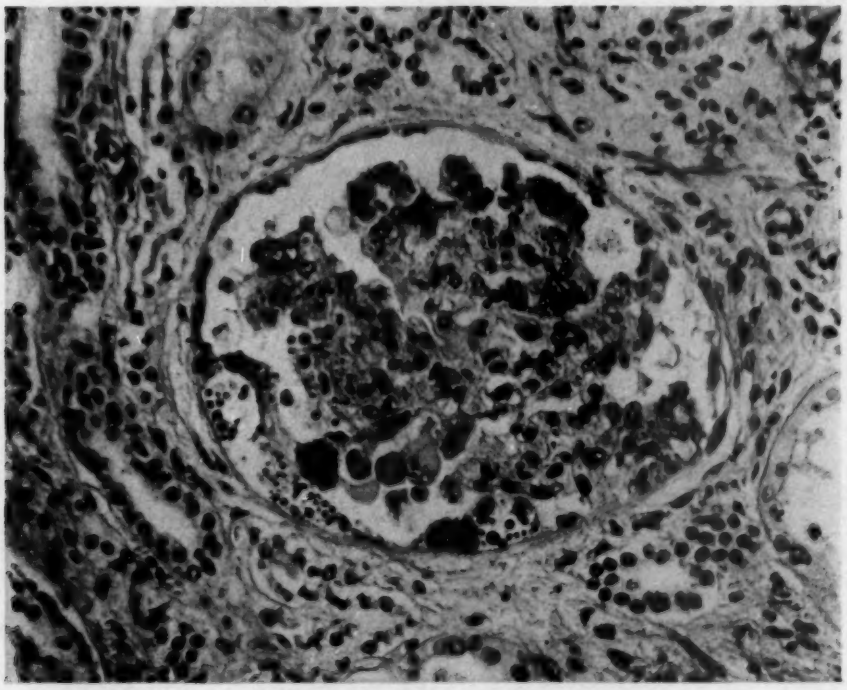

Fig. 12 (case 2).—Glomerulus showing epithelial proliferation and severe hyaline droplet degeneration.

desquamation, even with occasional crescent formation and slight accumulation of leukocytes within the capillaries, are a constant feature in the microscopic observations (figs. 11, 12, 13 and 14). These glomerular lesions exactly correspond with the descriptions and pictures given by Fahr, even in details. For instance, the hyaline droplet formation of the glomerular epithelium stressed by him in his cases of malignant nephrosclerosis was never missed in our cases. Fahr considered all these changes as pathognomonic of nephrosclerosis with renal insufficiency. We, however, found sporadically analogous glomerular changes in cases of vascular renal diseases in which neither the clinical nor the

chemical examination of the blood revealed any evidence of a decreased secretory capacity of the kidneys. Similar observations were reported recently by McGregor.[39] In these sporadic instances, death was due to cerebral hemorrhage or to cardiac insufficiency or to an intercurrent disease. It is clear that these cases could not have been considered as benign decompensated nephrosclerosis, in which, according to Fahr,[20] occasional inflammatory glomerular changes are produced by the irritating action of retained metabolites. Therefore, we believe that the proliferative, degenerative and exudative alterations of the glomeruli are

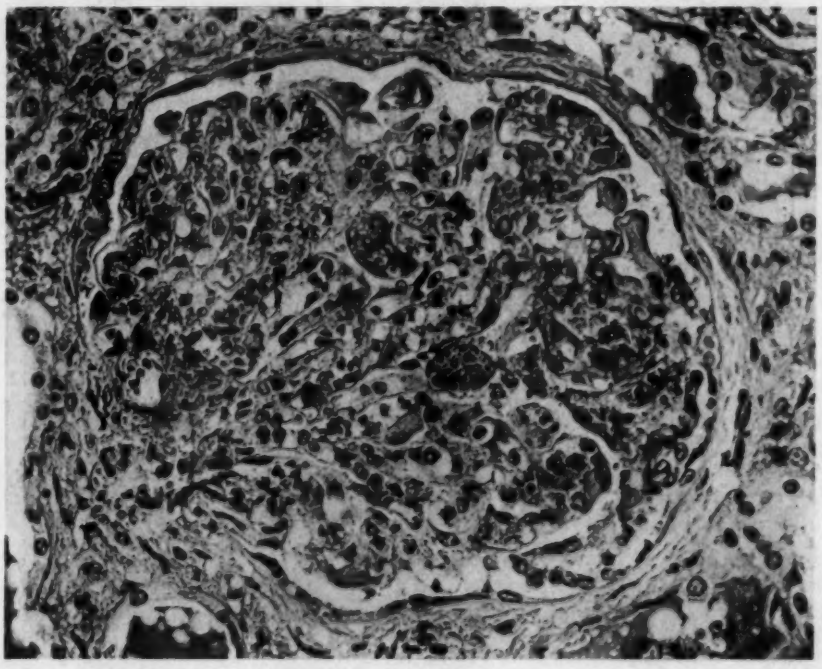

Fig. 13 (case 2).—Epithelial proliferation and desquamation, hyaline droplet degeneration and accumulation of leukocytes within the loops.

not specific for the vascular renal diseases with functional insufficiency. Because occasionally inflammatory glomerular changes were seen in cases without renal insufficiency it seemed important to us to learn how frequently such lesions were present in our cases with renal insufficiency. Differential counts revealed an average of only 10 per cent glomerular involvement. This seems to us proof that the focal glomerulitis cannot play a significant part in the causation of the renal insufficiency.

39. McGregor, L.: Histological Changes in the Renal Glomerulus in Essential (Primary) Hypertension, Am. J. Path. **6**:347, 1930.

The next question is whether we should consider these alterations as an evidence of a defensive inflammation in the sense of Aschoff [40] or as an expression of some other disturbance. The great majority of the malpighian corpuscles showed, according to our description, in every case, a conspicuous anemia of the capillary tufts. It seems logical to ask whether the ischemia, that is, inadequate blood supply, could be the cause not only of the degenerative but also of the proliferative alterations in the glomerular epithelium and of the slight leukocytic reaction as well. With this in mind, we examined many aseptic renal infarcts.

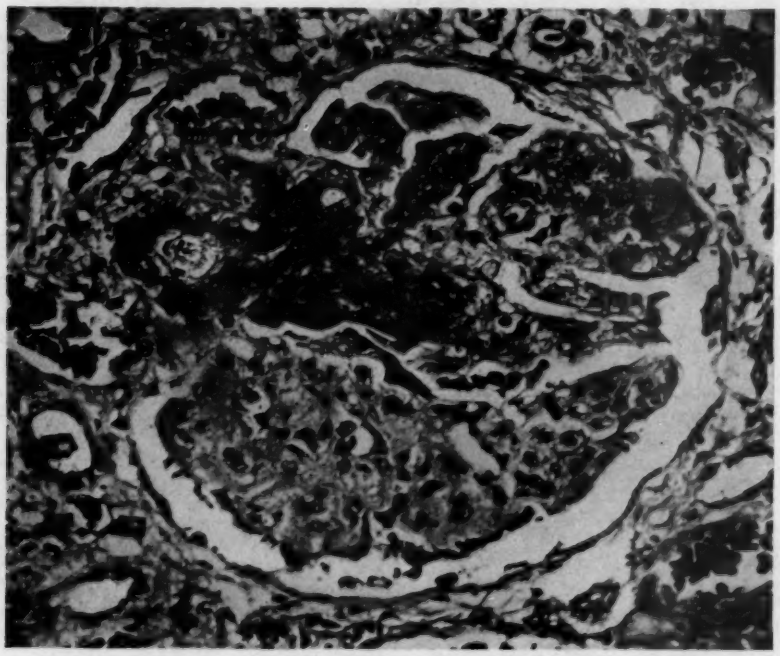

Fig. 14 (case 3).—Glomerulus showing the necrosis of loops and afferent artery and fusion of loops.

In their periphery, we saw, indeed, occasionally glomeruli that in every respect resembled the inflammatory glomeruli seen in our diseased kidney material. The ischemic origin of the former cannot be denied. These glomeruli also showed fatty and hyaline droplet degeneration in the glomerular epithelium in combination with the cell proliferation and occasional accumulation of leukocytes (figs. 15 and 16).

Having demonstrated that ischemia alone can produce these glomerular changes, we strongly suspect that an ischemic mechanism is responsi-

40. Aschoff, L.: Vorträge über Pathologie, Jena, Gustav Fischer, 1925.

ble for the identical glomerular alterations seen in malignant nephrosclerosis. We maintain that the epithelial proliferation is a compensatory reaction to the original epithelial damage brought on by inadequate blood supply, and that the accumulation of leukocytes within the loops is due to the chemotaxis of the necrobiotic cells, a process similar to that seen in the vicinity of aseptic infarcts. This explanation on the basis of ischemia has been urged by Jores,[12] Löhlein[25] and Volhard,[18] but controverted by Fahr[20] and von Mueller.[41]

Like Fahr and other authors, we found that the vascular lesions were the most conspicuous and characteristic alterations. The necrosis

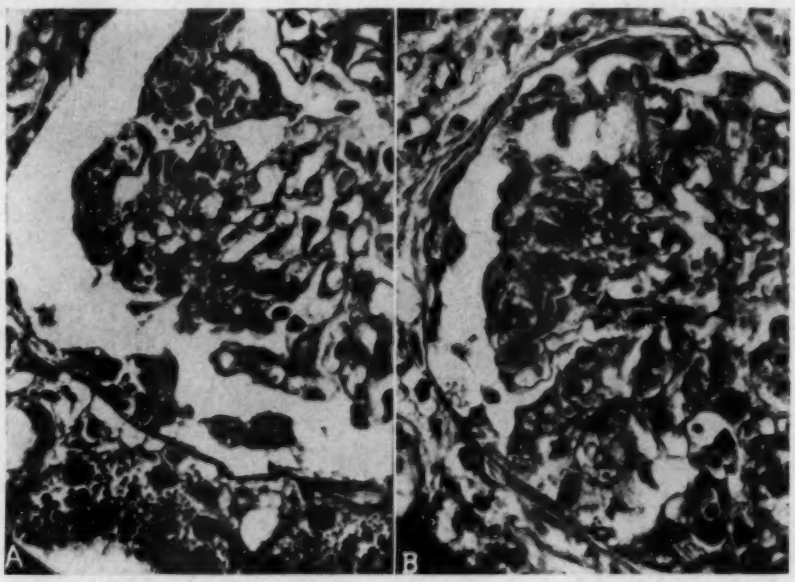

Fig. 15.—Glomeruli in the vicinity of an anemic infarct (in a case of aneurysm of the left ventricle). *A*, showing hyaline droplet degeneration of the external and internal glomerular epithelium and of convoluted tubules, and *B*, epithelial proliferation and hyaline droplet degeneration.

of the arterioles (vasa afferentia and distal portions of the interlobular arteries) can be sharply distinguished from the simple hyalinization. The indistinct limitation of the vessel wall, the aneurysmal dilatations and the impregnation of the vascular wall by red blood cells and the nuclear disintegration make it easy to distinguish one process from the other (fig. 17). Sudan stain, though it obscures the characteristic differential signs, is of great importance because it reveals the extreme

41. Mueller, F. von: Veröffentlichungen aus dem Gebiete des militäre Sanitätswesen, Berlin, A. Hirschwald, 1917, vol. 65, p. 45.

fatty degeneration of the arteriolar wall. The absence of leukocytic infiltration within and around the blood vessels is the second important feature of the necrotizing vascular lesions. On this point, our observations differ from those described by Fahr [20] and Hückel,[42] who emphasized the inflammatory reaction. Therefore we cannot follow Fahr, who believed that the arteriolar necrosis in malignant nephrosclerosis is identical with the necrotizing arteriolitis, as it occurs occasionally in subacute glomerulonephritis. The lesions in the latter disease always show a more or less extensive zone of leukocytic infiltration and fibrin

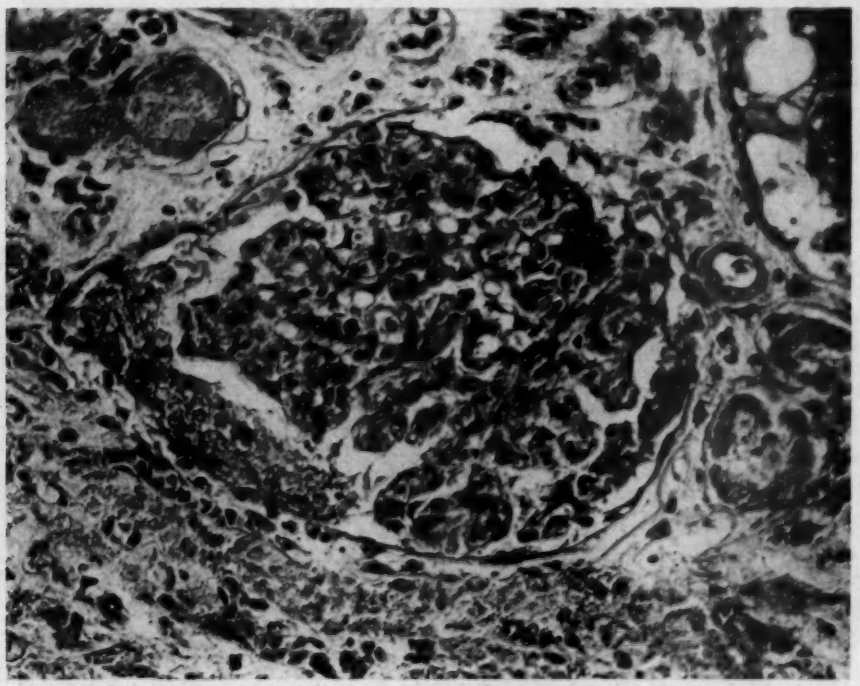

Fig. 16.—Glomerulus in the vicinity of an anemic infarct (in a case of carcinoma of the cecum) showing epithelial proliferation and desquamation and many leukocytes within the capillaries.

within the adventitia; these were never found in our cases. Furthermore, the fatty degeneration here is not as constant as in the necrotized arterioles in our cases. We found fatty degeneration always present and inflammatory changes always absent in the necrotizing arterioles in our cases of malignant nephrosclerosis. We therefore believe that the process is primarily degenerative and is an expression of a severe grade

42. Hückel, R.: Beiträge zur malignen Nephrosklerose, Virchows Arch. f. path. Anat. **276**:447, 1930.

of arteriolosclerosis. There is no doubt that the arteriolonecrosis is a constant and conspicuous feature of this group of cases with renal insufficiency, and it therefore serves as a valuable diagnostic criterion in the pathologic picture. For a long time we believed that it existed only in these cases. However, after prolonged investigation, we discovered arteriolonecrosis of the same type in cases of nephrosclerosis with severe arteriolar hyalinization in which there was not the slightest sign of renal insufficiency (fig. 18 *A*). It is true that this arteriolar necrosis is found only in an occasional vessel. Nevertheless, its occurrence under these circumstances proves that vascular necrosis cannot be pathognomonic of nephrosclerosis with renal insufficiency. Of course, the cause of the extreme degenerative vascular disease will

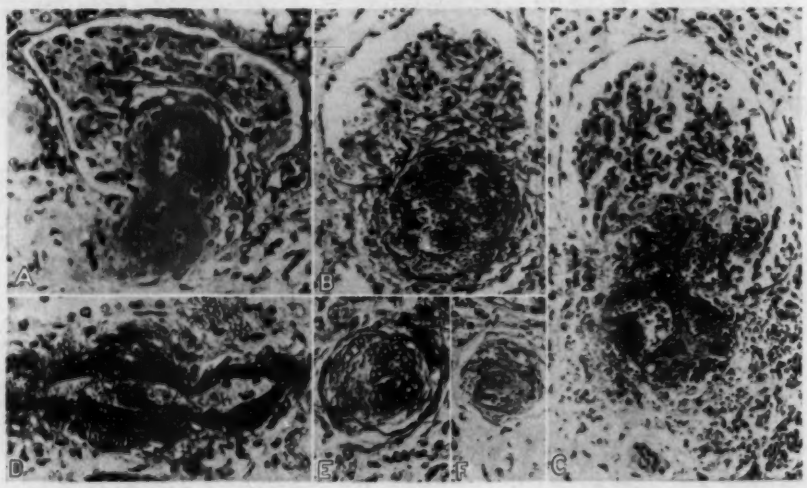

Fig. 17.—Arteriolar lesions from cases of malignant sclerosis, showing various phases of arteriolonecrosis. The wall is impregnated with red blood cells, which appear black in the reproduction, but there is no other cell infiltration. *A*, hyalinization of afferent vessel with beginning necrosis, evidenced by impregnation of vascular wall by red blood cells; *B*, aneurysmic dilatation and massive impregnation of wall of afferent vessel; *C*, rupture of necrotic afferent vessel, with perivascular hemorrhage; *D*, longitudinal section showing hyalinized vascular wall with necrosis and aneurysmic dilatation; *E* and *F*, cross-sections of intraparenchymal arterioles showing impregnation by red blood cells.

remain obscure as long as the cause of atherosclerosis in general is not known. However, in our opinion, it is likely that ischemia plays an important rôle as a secondary factor. We suggest this conception because we found arteriolonecrosis also in the periphery of aseptic renal infarcts (fig. 19).

The extreme narrowing of the entire vascular bed of the renal cortex is of the utmost importance in the pathogenesis of the cases presented

here (fig. 20). The frequent occurrence of anemic infarcts and small foci of tubular necrosis is due to focal thrombotic occlusion of severely damaged small blood vessels. The same cause is responsible for the multiple necrosis of the spleen and pancreas in three observations. The general interference with the glomerular circulation is apparent from the conspicuous anemia and collapse of the capillaries which is a significant feature of our observations. The occurrence of congested glomeruli seemingly contradicts this contention. In such instances, however, serial sections disclosed an obliteration of the afferent vessel at some point in its course (fig. 7). This is sufficient proof that the tufts could have been filled only by retrograde passage of blood from the venous side.

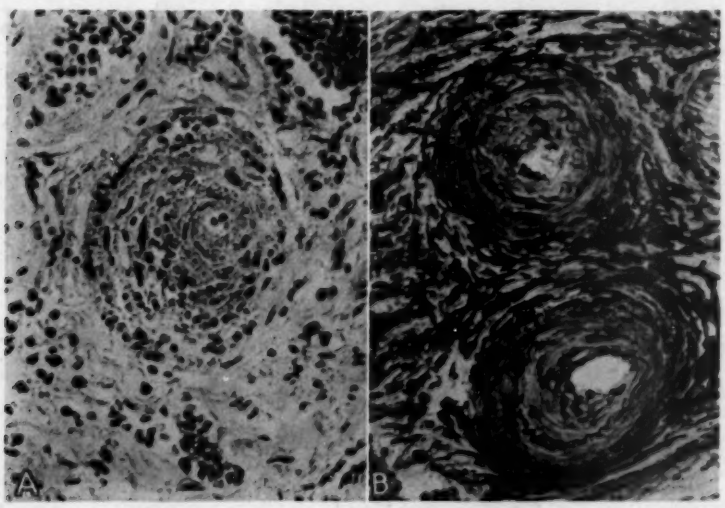

Fig. 18.—*A*, arteriolonecrosis in the kidney in a case of hypertension with fatal cerebral hemorrhage. *B*, the cellular intimal proliferation in the choroid in the same case.

The engorgement of the intertubular capillaries corroborates this contention. Furthermore, we have shown that the much disputed focal glomerulitis may be considered as a reactive phenomenon caused by ischemia. We believe that the arteriolonecrosis also is partly determined by the insufficient blood supply of the peripheral portions of the vascular tree. That constriction of the vascular bed takes place has been demonstrated by the renal injections of Baehr and Ritter,[43] in cases of the type here presented. These authors showed that the lumen of the interlobular arteries was impermeable to a barium-gelatin mixture which could pass the normal ramifications of the cortical vessels up to the

43. Baehr, G., and Ritter, A. S.: The Arterial Supply of the Kidney in Nephritis, Arch. Path. **7**:458, 1929.

capillaries. It is not difficult to realize that the insufficient blood supply of the cortex seriously affects renal function. This conception is upheld by the striking fact that the kidneys in our observations showed neither extreme atrophy nor diffuse acute glomerular alteration. In fact, at the first glance, one is surprised to find an apparent incongruity between the severe functional damage and the state of preservation of the renal parenchyma.

The question now arises as to the nature of this vascular lesion. The constriction of the lumen is caused, as we observed in every case, by a cellular proliferation of the intima, the breadth of which exceeds

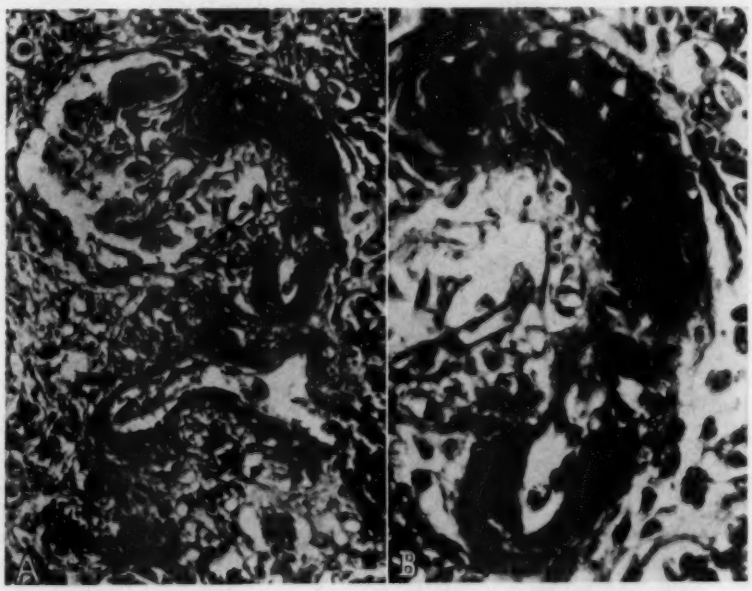

Fig. 19.—*A*, necrosis of the vas afferens in the vicinity of an anemic infarct (in the same case as the lesions depicted in figure 15). *B*, same under higher magnification. Note the hemorrhagic impregnation of the wall.

by far that of the media. The cells are fibroblasts, which often show a reticulated arrangement, and mononuclear cells with a large amount of fat (foam cells) (fig. 21). Between the cells, one encounters fine fibers that stain red with van Gieson's and blue with Mallory's connective tissue stain. Often there is in addition a distinct ground substance which in hematoxylin-eosin preparations takes a bluish color resembling the blue hue of embryonal connective tissue. The internal elastic lamella forms an uninterrupted delicate line separating the thickened intima from the media. This, however, holds only for the smaller branches. The larger vessels often show an outer zone of thickened intima which is denser and contains less cells but more collagen fibers.

In sections showing elastica, this zone presents numerous coarse concentric elastic fibers characteristic of elastica lamellation, whereas the inner zone of the intima shows only occasional fine elastic fibrils. There

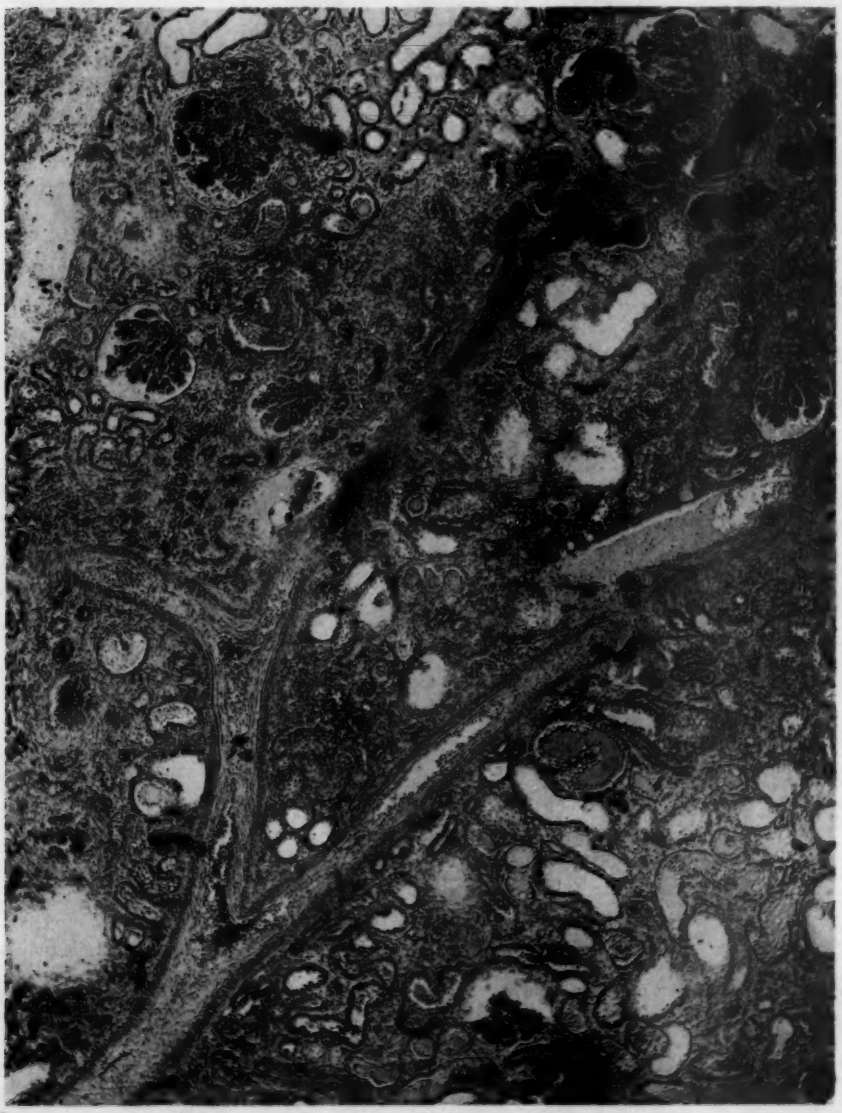

Fig. 20.—Ramification of an interlobular artery showing narrowing of the lumen by cellular intimal thickening, fatty infiltration and necrosis of the arteriolar endings and vasa afferentia. The glomerular lesions are anemia and hemorrhagic infarction due to complete closure of the afferent arteriole. Sudan-hematoxylin stain was used.

are always cross-sections and longitudinal sections of vessels that present marked elastica lamellation and connective tissue proliferation with marked narrowing of the lumen, which differ in no way from the familiar picture of simple atherosclerosis. These conspicuous vascular lesions (fig. 21) conform fully with the descriptions and figures of Fahr, who attaches great importance to them. These lesions Fahr designated as productive endarteritis, and he held that they are of inflammatory origin. It is our opinion that these vascular changes are not inflammatory, and therefore we must analyze the condition in greater detail.

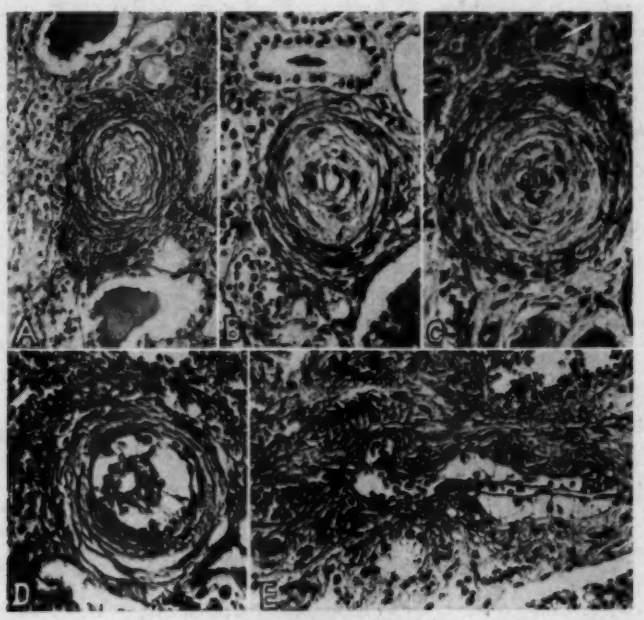

Fig. 21.—*A*, *B* and *C*, various pictures of the extreme obliteration of the lumen of the interlobular arteries by cellular intimal thickening. Note the lipophagic cells (foam cells) below the endothelium in *D* and *E* and the fine newly formed elastic fibers in *A*.

Connective tissue intimal proliferation differing from atherosclerosis because of the absence of an elastic hyperplastic external zone occurs, as is well known, in various pathologic vascular conditions. Friedländer [44] described alterations of the small vessels in chronically inflammatory territory and termed them endarteritis obliterans. One encounters such pictures daily in chronic peptic ulcers of the stomach, chronic cholecystitis, chronic pulmonary suppuration, etc. Although

44. Friedländer, C.: Ueber Arteritis obliterans, Centralbl. d. med. Wissensch. **14**:65, 1876.

the alteration of the intima is the most conspicuous feature of the process, the other coats of the vessel are also involved. The physiologic obliteration of the lumen of the ductus arteriosus or of ligated vessels is brought about by endothelial and fibroblastic proliferation. Damage to the outer coats of the vascular wall, such as trauma, mesarteritis or periarteritis, causes a reactive intimal proliferation often even beyond the affected area of the external wall of the vessel. The actual existence of a primary and isolated productive endarteritis is still controversial. It is clear that in our observations none of the mechanisms mentioned applies to the thickening of the intima. The inflammatory reaction of the stroma of the kidney, though generally present in our cases, is so clearly a reaction to the severe degenerative parenchymatous changes produced by the ischemia that it cannot be the cause of the vascular constriction. This is also clear because the vascular lesions are distributed independently of the inflammatory infiltration of the stroma, and because their intensity bears no relation to the severity of the inflammation of the stroma. Inflammatory lesions in the media or in the adventitia of the cortical arteries were always absent, as proved by serial sections, and could not have produced a reactive proliferation of the intima. The intimal thickening of the interlobular arteries in secondary contracted kidneys has been considered by several authors as being the result of the glomerular fibrosis (Fishberg,[45] and Baehr and Ritter [43]), analogous to the endarterial obliteration proximal to an amputation or a ligation. If this were true, vascular lesions should be found in every case of chronic glomerular nephritis and also in amyloid contracted kidneys; this is not the fact. However, apart from this argument, because glomerular fibrosis was rare in every case, for our cases this origin of the intimal proliferation cannot be considered at all. For the aforestated reasons we believe that the term productive endarteritis should not be applied to the intimal proliferation seen in our cases, because it implies the assumption of a pathogenesis that does not hold true for these vascular alterations.

The absence of a lamellated internal elastic layer in the smaller vessels is apparently the only feature that differentiates the lesion in question from atherosclerosis. Sudan stain reveals mostly fatty degeneration of the newly formed layer of cellular connective tissue which appears sometimes as a concentric ring between media and intima. We have mentioned that in some instances and particularly in those in which more advanced glomerular fibrosis occurred, we encountered newly formed elastic fibers in the outer zone of the thickened intima. Fahr [20] described similar observations and referred to them as a com-

45. Fishberg, A. M.: The Arteriolar Lesions of Glomerulonephritis, Arch. Int. Med. **40**:80, 1927.

bination of elastic hyperplastic thickening of the intima and endarteritis (his cases 51, 52, 54 and 55). It seems to us that these pictures allow different interpretations, if the deductions of Hueck [46] regarding the morphologic development of atherosclerosis are followed. His ideas center around the conception that the intima retains throughout life the embryonal mesenchymal character of a reticulated cytoplasmic syncytium. Under normal conditions, the meshes of the reticulum are collapsed. The first phase of atherosclerosis consists in an opening up of the reticulum whereby nuclei float from the "accessoria" (media and adventitia) into the cytoplasmic syncytium. This leads then to a thickening of the intima, which appears in cross-sections and longitudinal sections as a richly nucleated cytoplasmic network. The cytoplasm around the nuclei is condensed and becomes differentiated into nuclear cytoplasmic territories and cytoplasmic ground substance (endoplasma and ectoplasma of Hansen [47]). Immediately a fibrillar differentiation begins within the ground substance, leading to the formation of an argyrophil fiber, the silver or mesenchymal fiber of Ranke.[48] Connective tissue and elastic fibers are formed by impregnation of the fibrillar differentiation products by collagen or elastin. This takes place only gradually. In contradistinction to Jores,[49] Hueck maintained that the elastic lamellation does not occur by splitting up of the internal elastic lamella, but by actual new formation of elastic fibers from the cytoplasmic ground substance. In its first stage, the atherosclerotic intima would appear, therefore, as a mere cellular layer with beginning fibril formation between the mutually connected cells. This statement is not unsupported; in fact, Jores himself, in his classic monograph [49] in 1903, seventeen years before Hueck, stated that in the early phases of atherosclerosis he occasionally came on a pure cellular intimal thickening above an area of fatty degeneration at the border-line between media and intima. Our observations seems to coincide fully with the conceptions of Hueck as outlined here. We have emphasized the cellular constitution of the intimal proliferation (fig. 21 *B* and *C*) and have mentioned the delicacy of the collagen fibers, also the embryonal appear-

46. Hueck, W.: Anatomisches zur Frage nach Wesen und Ursache der Arteriosklerose, München. med. Wchnschr. **67**:535, 1920; Ueber das Mesenchym, Beitr. z. path. Anat. u. z. allg. Path. **66**:330, 1920.

47. Hansen, F. C. C.: Ueber die Genese einiger Bindegewebssubstanzen, Anat. Anz. **16**:417, 1899.

48. Ranke, O.: Neue Kenntnisse und Anschauungen von dem mesenchymalen Syncytium und seinen Differenzierungsprodukten unter normalen und pathologischen Bedingungen, Sitzungsb. d. Heidelberg. Akad. d. Wissenschaft., math.-naturwissensch. Kl., sec. B, 1913, Abhandl. 3; Zur Theorie mesenchymaler Differenzierungs- und Impregnations Vorgänge, ibid., 1914, Abhandl. 2.

49. Jores, L.: Wesen und Entwicklung der Arteriosklerose auf Grund anatomischer und experimenteller Untersuchungen, Wiesbaden, J. F. Bergmann, 1903.

ance of this connective tissue. With Bielschowsky's stain, the differentiation of the fibrils is more pronounced than with Mallory's or van Gieson's stain. This means that the impregnation by collagen is as yet not very advanced. We have, however, noted that often the connective tissue formation has progressed further and that the intimal proliferation in some instances seems to be much denser, containing far more collagen fibers. The appearance of elastica lamellation in the outer zone of this intimal layer (fig. 21 *A*) indicates the further development of the process, that is to say, a later phase of the atherosclerosis initiated by a purely cellular (better, cytoplasmic) intimal proliferation. The elastica differentiation represents a later phase of this process; we found it

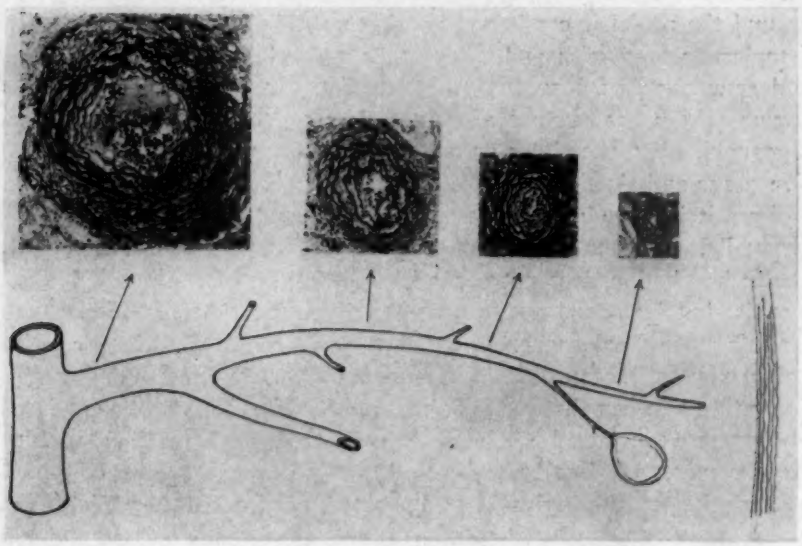

Fig. 22.—The entire course of an interlobular artery, showing the various phases in the development of atherosclerosis in one and the same vessel.

especially in cases of more advanced glomerular fibrosis, namely, those instances that indicate a longer duration of the pathologic vascular processes. Atherosclerosis is generally of slow development, and one is accustomed to seeing only the end-stages with the fully developed elastic hyperplastic connective tissue intimal thickening. The fact that we are able to demonstrate all the phases of the process, often in a single specimen (fig. 22), indicates that the process develops rapidly. We believe that we are warranted in asserting that the vascular alterations in malignant nephrosclerosis formerly and usually designated as endarteritis are in reality an accelerated form of atherosclerosis, in other words, an acute variation of the usually slow atherosclerosis of the small arteries.

Although the etiology of this accelerated form is no clearer than that of atherosclerosis in general, there is a special interest in speculating on the etiologic relationship in this type between our strictly morphologic observations and the conceptions put forth by Volhard. He believed that the alteration of the interlobular arteries in similar cases is dependent on a permanent vascular constriction which leads to an ex vacuo proliferation of the endothelium distally to the constriction. This proliferation acts to adjust the vascular lumen to the diminished volume of the circulating blood. Our studies show that an initial cellular phase is transformed by the gradual development of collagen and elastic fibers into atherosclerosis. On the other hand, we sometimes encountered in hypertension a simple atherosclerosis which disclosed a few small vessels presenting pictures of cellular intimal thickening resembling that described extensively in foregoing paragraphs (fig. 18 *B*). If vascular spasms are actually responsible for the initiation of the intimal thickening which, according to our opinion, is the first phase of atherosclerosis, it is conceivable that the etiologic difference between the two forms of the atherosclerotic processes lies in the severity and especially in the permanence of the vascular constriction (Volhard [50]). It is conceivable that a constitutional or acquired angiospastic factor could be the reason for the severity and specially for the acceleration of the vascular process which is the outstanding characteristic for the differentiation between vascular diseases of the kidney with and without functional insufficiency. We believe that the acceleration of the atherosclerotic process in the small cortical arteries of the kidneys is the essential pathogenic principle in our cases and leads subsequently to ischemic damage of the arterioles and glomeruli. Our observations are in accord with Löhlein's idea that the tempo of the atherosclerotic process distinguishes both forms of vascular nephrosclerosis. We also hold with Jores that the vascular alterations in these cases with renal insufficiency are far more extensive than in simple nephrosclerosis without functional damage. We, however, believe that the intensity of the lesion in the interlobular arteries is of primary importance, and not that in the vasa afferentia.

However, it would be a mistake to disregard the observations of Fahr and Hückel of definite inflammatory vascular changes in cases of identical clinical course and identical gross anatomic appearance. We have two cases to illustrate this point.

Case 17.—*History.*—A. C., a white man, aged 42, married, a salesman, was admitted to the hospital on Aug. 10, 1927. The family history was irrelevant. The childhood history was unimportant. Three years before, the patient felt fatigued. Albumin was found in the urine. The patient was told to cut down his

50. Volhard, F.: Der arterielle Hochdruck, Verhandl. d. deutsch. Gesellsch. f. inn. Med. **35**:134, 1923.

protein diet, which he did not do. He had occasional occipital headaches. Three weeks before, he noticed a bad taste in his mouth and had paroxysmal pains in the left lumbar region. His vision became blurred. He vomited twice in the two weeks previous to admission.

Examination.—On admission, he appeared to be chronically ill, was subicteric and showed puffiness of the eyelids. The breath was uriniferous. The heart was enlarged. The fundi showed neuroretinitis. The blood pressure was 200 systolic and 114 diastolic.

The urine was decreased in amount and contained albumin (++); the sediment contained granular casts, white blood cells and red blood cells. The con-

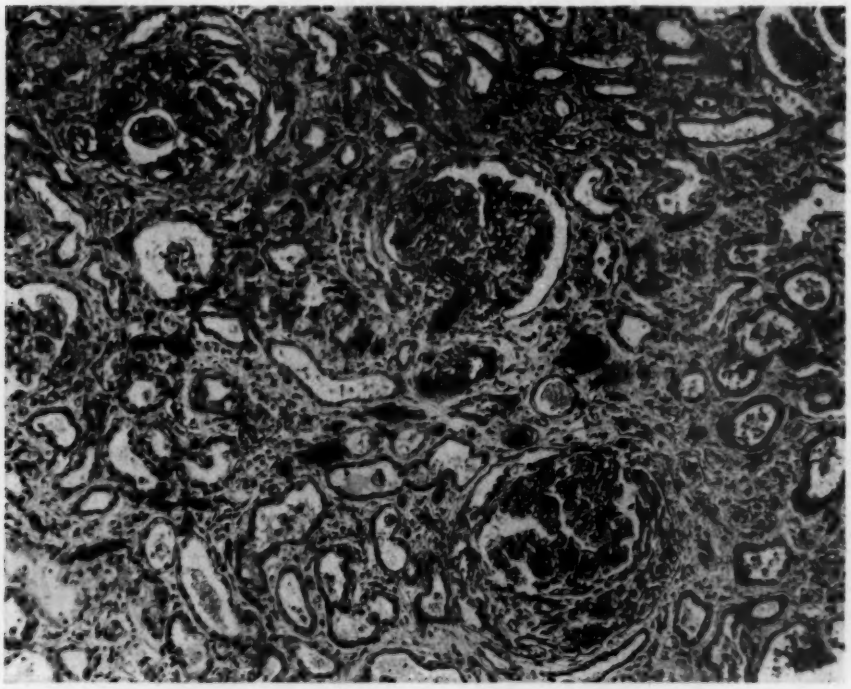

Fig. 23 (case 17).—Three glomeruli with inflammatory changes in one field and arteriolonecrosis.

centration was from 1.006 to 1.011. The phenolsulphonphthalein excretion was 10 per cent in four hours. The urea nitrogen of the blood was 91 mg., and the uric acid, 8.4 mg. per hundred cubic centimeters. The Wassermann reaction was negative. The blood count showed: hemoglobin, 44 per cent; red blood cells, 2,570,000; white blood cells, 8,900; polymorphonuclear leukocytes, 83 per cent; lymphocytes, 15 per cent; monocytes, 1 per cent, and eosinophils, 1 per cent.

Course.—The patient received a transfusion. Afterward he began to vomit uncontrollably. He died suddenly on August 16, after a paroxysm of coughing

Necropsy.—Eight hours after death, necropsy was performed by Dr. Klemperer. Permission to open the head was not obtained. The right kidney weighed 220 Gm.; the left, 200 Gm. The capsule stripped easily revealing numerous fine

yellowish granules and red pinpoint-sized hemorrhages. On section, the cortex appeared narrowed and the markings indistinct with a mottling of yellow and gray spots. The renal artery did not show changes.

Microscopically, nearly all of the glomeruli showed changes characteristic of an intracapillary subacute glomerulonephritis as: nuclear increase, many polymorphonuclear leukocytes, fusion of loops with each other, as well as with Bowman's capsule, and proliferation and desquamation of glomerular epithelium with occasional crescent formation (fig. 23).

The stroma was diffusely increased and infiltrated with lymphocytes, polymorphonuclear leukocytes and occasional plasma cells. The tubules contained desquamated epithelial cells, leukocytes and granular casts. The epithelial cells often

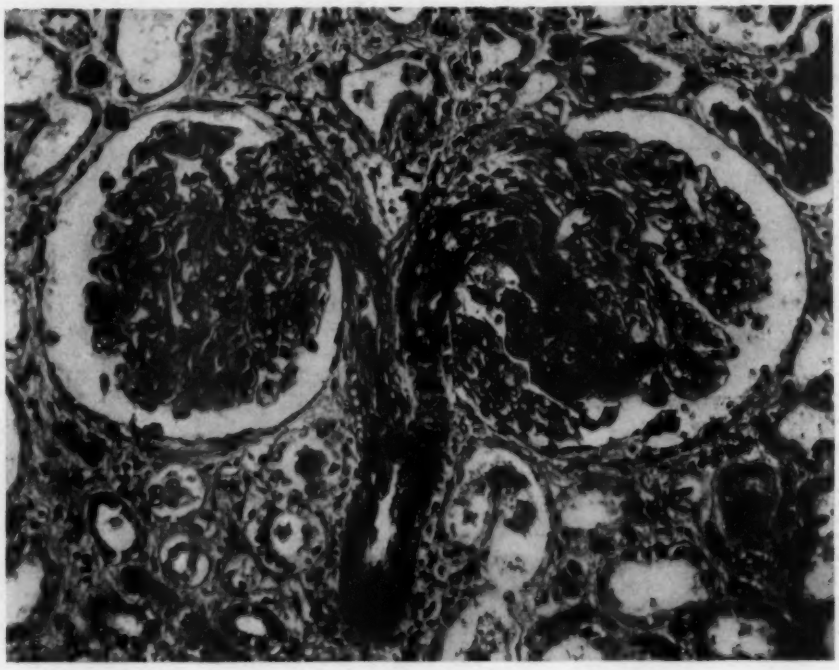

Fig. 24 (case 17).—Necrosis of an afferent vessel, with perivascular leukocytic infiltration.

showed hyaline droplets and fat. They were frequently flattened and had lost their characteristics. The most conspicuous change was necrosis of the capillary loops, arterioles and small branches of the interlobular arteries. The necrotic vessels were surrounded by an infiltration of polymorphonuclear leukocytes, polyblasts and lymphocytes (fig. 24). The perivascular infiltration and necrosis were occasionally so marked that the picture simulated that found in larger vessels in periarteritis nodosa. The interlobular arteries often showed thickening of the intima, which was infiltrated by polymorphonuclear leukocytes, lymphocytes and polyblasts (fig. 25). The larger vessels showed atherosclerosis. Sudan stain revealed only moderate fatty degeneration of the arteriolar wall. Bacterial stains were negative.

Diagnosis.—The diagnosis was: subacute glomerulonephritis with arteriolonecrosis; hypertrophy of the left ventricle; edema of the lung, and ascites.

CASE 18.—*History.*—E. J., a colored woman, aged 40, married, a housewife, was admitted to the hospital on April 2, 1927. The family history was irrelevant. The patient had always been well, but two years before admission, she was told that she had high blood pressure. She was advised to keep to a diet, which was, however, not strictly adhered to. For some time she had had dyspnea on moderate exertion. For three months she had had frequent headaches. She became pregnant and vomited frequently within the first months. Two weeks before admission, she went to bed because of an aggravation of her symptoms,

Fig. 25 (case 17).—Arteriolonecrosis and arteritis of an interlobular artery. Note the inflammatory cells within the proliferated intima.

and a few days later she aborted. Then she became drowsy, fell into stupor and was admitted to the hospital in coma.

Examination.—She had no fever. She had Cheyne-Stokes' respiration and a urinous breath. Her blood pressure was only 124 systolic and 70 diastolic, but she was already in extremis. Her urine contained albumin (+); the sediment, clumped blood cells and granular casts.

The urea nitrogen of the blood was 169 mg. per hundred cubic centimeters. The white blood cells numbered 15,400; the polymorphonuclear leukocytes, 86 per cent, and the lymphocytes, 12 per cent. The Wassermann reaction was negative.

Course.—The patient died on April 3.

Necropsy.—A few hours later necropsy was performed by Dr. Klemperer. The right kidney weighed 175 Gm.; the left, 160 Gm. The capsule stripped with fair ease, revealing a finely granular surface, studded with an enormous number of irregular hemorrhages varying in size from that of a pinpoint to that of a pinhead and larger and numerous yellow pits. On section, the cortical markings were obscured by numerous small infarcts and hemorrhagic flecks. The small arteries were prominent.

Microscopically, the cortex was studded with numerous areas of necrosis which left little unaffected renal parenchyma. In such areas, however, some glomeruli were large, with delicate engorged capillary loops; other glomeruli, however, showed a few necrotic loops, nuclear increase and epithelial proliferation. Here

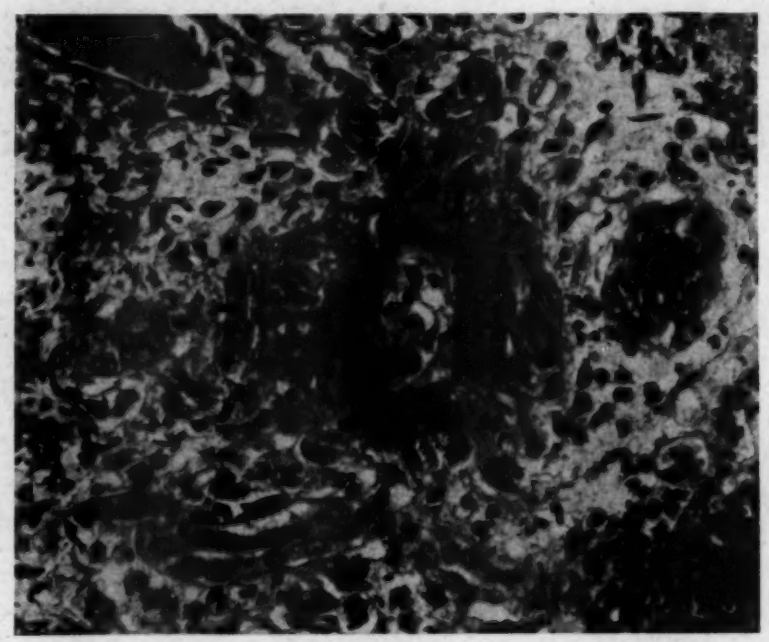

Fig. 26 (case 18).—Arteriolonecrosis with perivascular cellular infiltration and fibrin infiltrating the wall extending into the adventitia.

the arterioles showed marked hyalinization and necrosis. The blood vessels supplying the areas of necrosis showed necrosis and severe perivascular infiltration with polymorphonuclear leukocytes and lymphocytes (fig. 26). They were often thrombosed. Bacterial stains were negative.

The spleen and the liver showed marked hyalinization of the arterioles. The pancreas and the suprarenal glands showed an extreme degree of arteriolosclerosis. Within the pancreas, several larger arteries showed necrosis with infiltration of the vascular wall and the adventitia by polymorphonuclear leukocytes and thrombosis (fig. 27). The pancreatic tissue around the vessel was necrotic. Within the suprarenal gland, one artery showed an identical picture.

Diagnosis.—The diagnosis was: arteriolosclerosis and arteriolonecrosis of the kidneys with multiple infarctions; circumscribed necrosis of the pancreas; hypertrophy of the heart, especially of the left ventricle, and status after abortion.

The clinical course in these cases resembled that in our other cases. After an antecedent stage of hypertension of several years' duration, the middle-aged patients suddenly developed symptoms of renal insufficiency and died in uremia. The gross morphology of uncontracted kidneys with conspicuous hemorrhages was also in agreement with the observations in our other cases.

The arterial lesions were also the outstanding features of the microscopic picture. These differed, however, from those previously described in the character of the necrosis; for we found severe inflam-

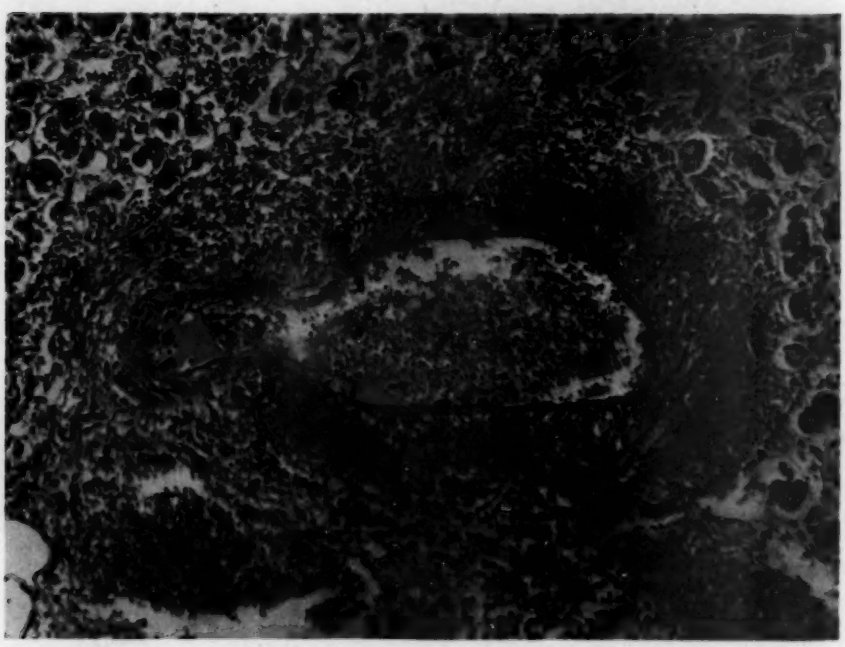

Fig. 27 (case 18).—Pancreatic artery showing necrosis of media and inflammation as in periarteritis nodosa.

matory reaction within and around the vessels. These alterations could truly be designated as necrotizing arteriolitis, endarteritis and periarteritis. The further difference consisted in a diffuse glomerulitis in the first case and the presence of a necrotizing arteritis in the pancreas and suprarenals in the second case. It seems significant that we encountered the necrotizing arteritis only in these two cases in which there was also present a morbid process recognized generally as toxic in origin. We refer to the subacute glomerulonephritis in case 17 and to the hyperemesis gravidarum in case 18. In both cases there were shown severe hyalinization of the arterioles and advanced atherosclerosis of the small arteries, widely distributed in case 18. It is possible that this antecedent

vascular damage made the arterioles and arteries more vulnerable to the influence of toxin and in this way acted as another determining factor for the vascular necrosis (Herxheimer [21]). Of course, we appreciate that necrotizing arteriolitis is not so rarely found in subacute glomerulonephritis. However, we have encountered it only in cases of so-called "stormy course" of Löhlein [51] with the characteristic histologic picture of extracapillary glomerulonephritis. The fact that the glomerulitis in case 17 was mainly intracapillary, therefore of the milder type, supports the implication that the antecedent vascular damage is an important factor.

A comparison of our observations and the reports in the literature showed clearly that cases of identical clinical course present a definite difference in the type of the essential vascular alteration. A careful analysis disclosed the degenerative nature of the arteriolonecrosis and of the so-called endarteritis of the small cortical arteries in the overwhelming majority of our observations. On the other hand, one cannot doubt the inflammatory nature of the periarteritis and endarteritis of the interlobular arteries and the necrotizing arteriolitis of the vasa afferentia in the cases reported by Fahr and Hückel and in one of our own cases. This clearly indicates that the anatomic picture of the kidneys in the malignant phase of hypertension must be divided accordingly into an accelerated atherosclerotic and an arteritic form.

ETIOLOGY

Fahr postulated a toxic etiology for his cases and considered, mainly, syphilis, lead and rheumatic polyarthritis as the causative agents. Hückel's cases were also syphilitic. In one of our cases of the arteritic form there was evidence of a toxic factor, though not of the same nature as Fahr contended, which superimposed on previously damaged vessels might have been responsible for the severe vascular lesion. In the other cases, however, only one of the patients had a positive Wassermann reaction and he had no syphilitic organic lesion; another patient had previously had lead poisoning. None of the patients had a history of either polyarthritis or an acute or a chronic valvular disease suggestive of rheumatism. This conspicuous difference in the etiology of our series is a further foundation for our view in distinguishing two forms of malignant nephrosclerosis. Some of our patients had suffered from occasional headaches a long time before the onset of their severe symptoms. Of course, we cannot maintain that these were an evidence of an angiospastic migraine. We would therefore like to recommend that similar cases should be investigated as cautiously and carefully as pos-

51. Löhlein, M.: Ueber die entzündlichen Veränderungen der Glomeruli der menschlichen Nieren, Arbeiten a. d. path. Institut zu Leipzig, 1908.

sible for antecedent angiospastic symptoms. We offer the suggestion that such a constitutional or acquired factor may be responsible for the accelerated atherosclerotic type of malignant nephrosclerosis.

DIFFERENTIAL DIAGNOSIS

It is evident that in the differential diagnosis we have to consider only cases with hypertension and uremia without edema. In essential hypertension of longer duration, almost invariably arteriolosclerosis of the vasa afferentia is present, combined with atherosclerosis of the arcuate and interlobular arteries. This vascular alteration produces atrophy of the parenchyma which may reach such an extent as to cause excretory insufficiency. Such instances have been designated by Fahr as benign decompensated nephrosclerosis. The decompensation may be absolute, owing to parenchymal destruction so extensive that the remaining renal rest is unable to take care of the waste products, or it may be relative, owing to the simultaneous cardiac insufficiency. In such instances, the renal destruction is not advanced enough to cause functional insufficiency as long as an increased cardiac action compensates by increasing the velocity of the perfusion fluid. In both events, however, the decrease in the size of the kidneys and the more or less advanced glomerular fibrosis is sufficient evidence of the prolonged vascular alterations which had gradually caused the atrophy. In contradistinction to this picture, the kidneys in the malignant phase of hypertension are generally not shrunken. They show, however, in addition to a diffuse irregular flat granulation, characteristic ecchymoses, as gross evidence of the hemorrhage due to the severe vascular lesions.

The glomerular fibrosis is never marked. The extreme diffuse alteration of the small cortical vessels, as described, together with the secondary ischemic phenomena of arteriolonecrosis and focal glomerulitis are the features that histologically distinguish the accelerated atherosclerotic form from the simple, gradually developing renal atherosclerosis and arteriolosclerosis with renal insufficiency. It is clear that the arteritic form of the malignant phase of hypertension cannot be confused with simple atherosclerosis.

Chronic glomerulonephritis with atrophy, the secondary contracted kidney, offers in the majority of cases no differential diagnostic difficulties. The development of conspicuous vascular changes, however, may cause, in some instances, grave doubts as to the proper interpretation. This holds true especially for cases in which the glomeruli do not show diffuse involvement, but in which the alterations of the arcuate and interlobular arteries are striking. The vascular lesions in chronic glomerulonephritis are commonly divided into true atherosclerosis and endarteritis. It has been generally accepted within the last years that

the explanation of the development of atherosclerosis in chronic glomerulonephritis lies in the permanent increase in the blood pressure. The so-called endarteritic process, however, has been explained as the result of the chronic inflammation or of the destruction of parenchyma. Volhard assigns to this process the pathogenesis mentioned heretofore, namely, a permanent vascular spasm. It seems to us just as impossible to differentiate these vascular lesions in secondary contracted kidneys from those found in the malignant renal phase of hypertension, as it is impossible to distinguish between the atherosclerosis in chronic glomerulonephritis and that in essential simple hypertension. Since we believe that the so-called endarteritis in the former condition is only an accelerated form of atherosclerosis, we are of the opinion that its occurrence in chronic glomerulonephritis indicates only a more rapid tempo in the development of the atherosclerosis, but not a different pathogenesis. This conception is supported by the fact that degenerative arteriolonecrosis is also encountered occasionally. The histologic differentiation of such cases of chronic glomerulonephritis complicated by acute atherosclerosis of the interlobular arteries is sometimes exceedingly difficult. One can depend on the extent of the inflammatory glomerular involvement, which exceeds in these instances that encountered in the malignant renal phase of hypertension. Nevertheless, the interpretation may sometimes be subjective. It is imperative to examine many sections from various regions of the kidneys before reaching a diagnosis. Fortunately such cases are not too frequent. Among thirty-seven cases of chronic glomerulonephritis and malignant nephrosclerosis, we found only two that were doubtful pathologically.

CLASSIFICATION OF VASCULAR RENAL DISEASE IN HYPERTENSION

The extent and the intensity of the renal vascular alteration are responsible for two forms of hypertensive disease, one with and one without renal insufficiency. Accordingly, we may classify the concomitant renal process in three groups:

1. The slow progressive atherosclerosis of the vascular tree, primarily without contraction (atherosclerosis renum initialis lenta); secondarily with subsequent gradual atrophy of the renal parenchyma (nephrocirrhosis atherosclerotica lenta, with three subgroups according to the degree of contraction—incipiens, progressa or gravis).

2. The rapidly progressing diffuse atherosclerosis (nephrocirrhosis atherosclerotica accelerata, with only the first two subgroups according to the degree of contraction).

3. The inflammatory diffuse vascular lesion superimposed on an antecedent atherosclerosis (nephrocirrhosis atherosclerotica et arteritica with the same subgroups as in 2).

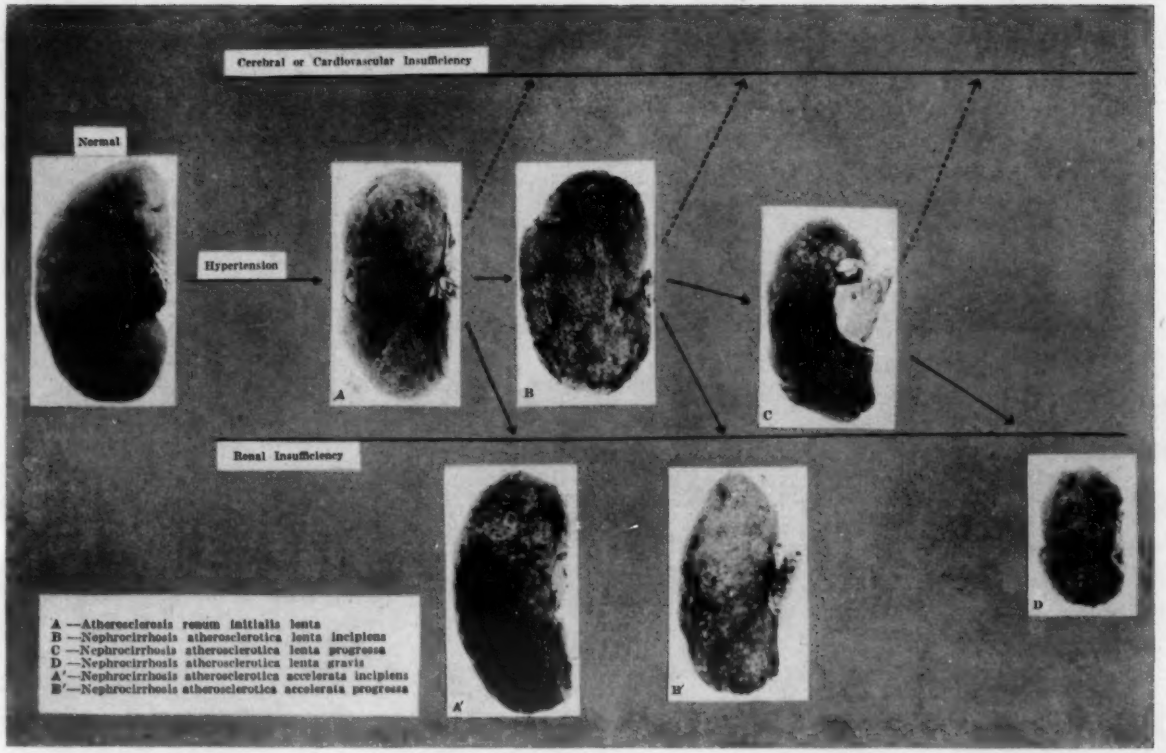

Fig. 28.—Schema of renal lesions in hypertension illustrated by actual cases. The arteritic form was not tabulated because there are no macroscopic features distinguishing it from the accelerated atherosclerotic group.

A differentiation of arteriolosclerosis and arteriosclerosis has been omitted because both processes have an identical pathogenesis and are too frequently combined to be separated by terminology (fig. 28).

The schema here set forth indicates that the atherosclerotic process may become accelerated at any phase of group 1, causing renal insufficiency. It is, however, conceivable that this change in the tempo may occasionally not be so rapid, and that such instances may form an intermediate group between groups 1 and 2. This assumption is suggested by cases 11, 12, 15 and 16, with more advanced atrophy than was found in our other observations but with less contraction than in the advanced forms of the lenta group.

SUMMARY

Essential hypertension with renal insufficiency is associated either with (1) the slowly progressing type of atherosclerosis manifesting a gradual constriction of the vascular bed and subsequent pronounced destruction of the functioning parenchyma, or (2) with a more rapidly developing vascular change in which severe renal atrophy is absent.

The latter form, the malignant renal phase of hypertension, must be divided on a pathologic basis with regard to the nature of the vascular lesions into (1) an accelerated atherosclerotic and (2) an arteritic form.

The rapidly developing obliteration of the vascular bed is responsible for the sudden onset of fatal renal insufficiency.

The etiology of the vascular condition is unknown. It is conceivable and in accord with Volhard's conception that a constitutional or acquired angiospastic factor plays a determining rôle in producing the accelerated atherosclerotic form. The arteritic form is most probably due to the effect of various toxins on vessels that have already suffered a simple degenerative atherosclerosis.

GANGLIONEUROMA OF RETROPERITONEAL ORIGIN

REPORT OF A CASE, WITH BIBLIOGRAPHIC REFERENCES TO NINETY-THREE SIMILAR TUMORS *

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PHILADELPHIA

H. D., a white girl, aged 12, was observed to have a gradually enlarging abdomen. When asked about it, she complained of no pain or other disturbance, nor could she in any way account for it. As the enlargement continued, the protuberant abdomen attracted attention more and more, and she was in due course of time charged with being pregnant. Her parents then took her to a physician, who made a careful physical examination that resulted in the discovery of an abdominal tumor not connected with the uterus, which was normal and infantile. As the tumor had apparently grown as rapidly as the fetus for which it was mistaken would have done, malignancy was feared and operation recommended.

This was performed in September, 1915, fifteen years ago, in a hospital in Trenton, N. J., by Dr. Edward Skillern Hawke, who found and removed a large nodular retroperitoneal mass that weighed about 4½ pounds (2 Kg.) and was thought to be a sarcoma.

The tumor, or parts of it, were sent to the laboratory of the State Hospital, where sections were prepared by Miss Mae I. Lovett. At that time the pathologist, Dr. Frederick Hammond, was in Europe, and had arranged to have slides of tumor tissues sent to me for identification.

I at once recognized the peculiar structure of the tumor and identified it as a "ganglionar neuroma." Miss Lovett, finding that I was interested in the case, sent me additional sections from different parts of the tumor. I thus came into possession of nine mounted slides, two stained with hematoxylin and eosin, two with thionine, one with Mallory's aniline blue, one with Mallory's phosphotungstic acid hematoxylin, one with van Gieson's stain and one by Pal's method.

Dr. Hammond returned from abroad ill; he soon became incapacitated and gave up his work, so that he was unable to act on my suggestion that he publish the case. A year or two later I wrote to Dr. Hawke suggesting that he publish the case, but received no answer. A request for some of the tissue, in order that more sections might be made, resulted in the discovery that the tumor had been thrown away. A later request for the loan of the paraffin blocks was answered by a letter saying that a new technician had taken Miss Lovett's place, and that the change had resulted in a good deal of material having been rejected as no longer useful; probably these blocks had been thrown away, as they could not be found.

From time to time correspondence with Dr. Hawke was renewed, with the object of having the tumor recorded, but he never replied, probably because, as was learned from other sources, the subject was very distasteful to him, the patient having died on the third day after the operation.

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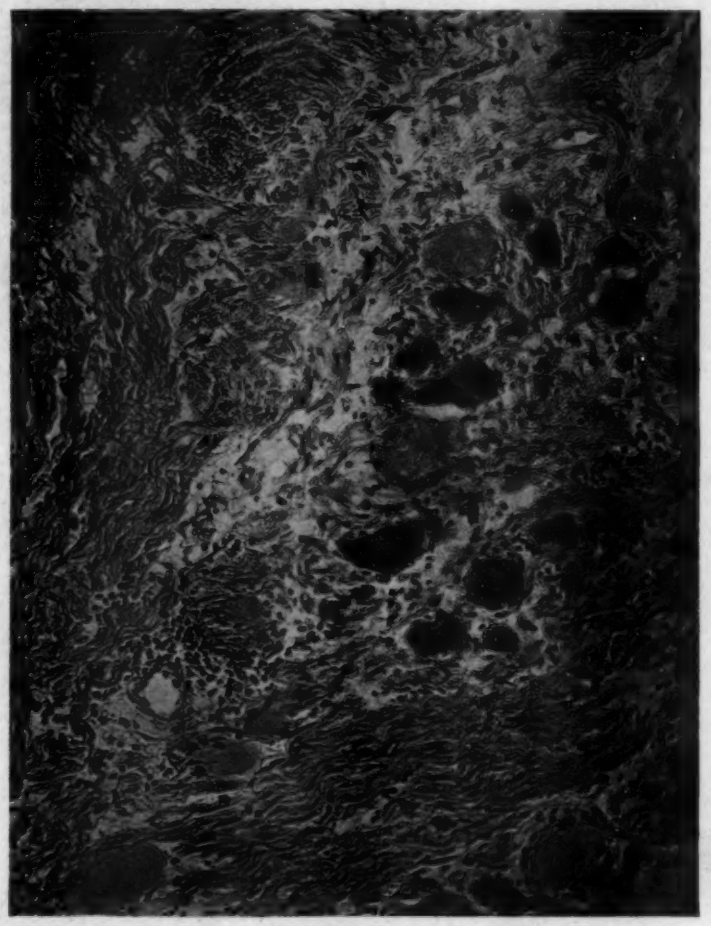
* Submitted for publication, June 30, 1930.

* From the McManes Laboratory of Pathology of the University of Pennsylvania.

So the matter dragged along until Dr. Hawke died.

The surgeon having passed away, the pathologist being permanently incapacitated and entirely uninterested, the technician having resigned and the material having been thrown away, there is no longer any one but myself sufficiently interested in the case or acquainted with it to place it on record.



Portion of the tumor showing a bundle of fibers in the lower part, another on the left, and a group of ganglion cells, some of which are in fair condition, while others are in a state of advanced degeneration such as is characteristic of the lesion. The wavy character of the bundles of fibers, together with their reaction to the specific stains, shows them to be a highly specialized type of tissue probably descended from the neuroglia. Although the fibers rarely contain axis cylinders, there is no doubt of their neurogenic origin.

Since 1915 there have been about twenty-eight publications dealing with the ganglioneuromas and reporting new cases, so that the tumor

is much better known than when the case under consideration came under observation. In nearly every one of the contributions there is a complete description of the histologic appearances, sometimes brief, but too often tediously long. It therefore seems unnecessary to burden the literature with another description of the tumor, the photomicrograph that accompanies this report being sufficient guarantee of the correctness of the identification. But those especially interested in ganglioneuromas may be glad to be furnished with a bibliography of the subject, and to that end one is appended. Two works may prove of special value: that of H. R. Wahl, in the *Journal of Medical Research* (**30**: 205, 1914) in which he deals with all varieties of nerve cell tumors, systematically arranging them, commenting on their relationships and including a lengthy bibliography; and that of J. S. Dunn in the *Journal of Pathology and Bacteriology* (**19**: 456, 1915), in which much the same ground is covered.

In looking over the more recent contributions, I discovered that the authors just referred to had missed some cases found by later students, and that some of the references had been incorrectly given. A complete review of the literature was therefore made. Unfortunately, a few of the references were to papers that proved to be inaccessible, so that although the following list is undoubtedly an improvement on previously published lists, it cannot be said to be perfect.

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Laboratory Methods and Technical Notes

A METHOD FOR STAINING LECITHINS IN SECTIONS*

C. M. Ramírez Corria, Havana, Cuba

The following technic for staining lecithins in sections is useful.

Frozen sections are placed in acetone, at room temperature, for from one to twenty-four hours. The sections are washed, and are then placed in sudan-acetone, for a few minutes. Then differentiation, washing, mounting, etc., are done. The nuclei stain as in ordinary sudan sections; the acetone soluble lipids are not stained, and the lecithins stain pale red or orange.

* Submitted for publication, Aug. 11, 1930.

* From the Sanatorio "La Purisima Concepción."

Notes and News

Cancer Survey of the United States.—According to *Science,* the U. S. Public Health Service will be able to begin at once its cancer survey, which is to include: (1) an investigation of the researches being carried on with respect to control of cancer in various institutions in the United States and abroad; (2) an investigation of existing methods of treatment of cancer with a view to determining and encouraging the use of the best methods of treatment to the exclusion of those that are worthless or fraudulent; (3) the ascertaining of the best methods of increasing the number of physicians skilled in the diagnosis and treatment of cancer; (4) the ascertaining of the best means of educating the public with respect to the signs and symptoms of cancer in early stages in order to prevent neglect and delay in treatment; (5) the ascertaining of the extent to which provision now exists for furnishing optimum treatment for cancer in all sufferers, together with an estimate of what would be needed to make this adequate, and the cost thereof; (6) the collection of any other pertinent data to enable Congress to act advisedly in this matter.

Window Method of Studying Living Tissue.—The method consists in the introduction of a transparent double wall or window into a small hole in the ear of a rabbit. One side of the window is celluloid or glass and the other mica; living tissue invades the chamber in a transparent layer which can be studied microscopically in vitro under various conditions. The Rockefeller Foundation has granted $15,000 a year for five years for the perfection and extension of the method.

University News, Appointments, Promotions, Resignations, etc.—Carl O. Günther, bacteriologist, one of Koch's assistants, and well known to early American students of bacteriology, has died at the age of 75.

E. D. Peasley, formerly of the department of pathology and bacteriology in the University of Iowa, is now pathologist to the Truesdale Hospital, Fall River, Mass.

In the school of medicine of the University of Kansas, S. D. Katz has been appointed instructor and T. J. Sims, Jr., and O. S. Randall assistants in pathology. T. J. Sims, Jr., also serves as resident pathologist in the Bell Memorial Hospital.

Theodore S. Kimball has been appointed assistant pathologist and John L. Jackson resident pathologist in the Los Angeles County General Hospital.

H. P. Smith, associate professor of pathology in the University of Rochester, N. Y., has been appointed professor of pathology in the University of Iowa.

W. C. Merkle, associate in pathology in the University of Maryland, has been placed in charge of the laboratories of the Union Memorial Hospital in Baltimore.

M. C. Porterfield has been appointed instructor in pathology in the University of Maryland.

In the University of California, J. F. Rinehart has been promoted to assistant professor of pathology and Hermann Becks has been appointed assistant professor in charge of dental pathology.

In the University of Nebraska at Omaha, Victor Norall has been appointed resident pathologist in the university hospital; J. T. Myers, associate professor of bacteriology, has been advanced to professor of bacteriology and public health.

Stokes' Tablet.—A memorial tablet in honor of William Royal Stokes has been erected in the municipal building in Baltimore by his fellow employees in the health department. The tablet bears the relief portrait of Dr. Stokes and this inscription: "To the memory of an able physician and bacteriologist. A lover of art, music and poetry, who died a martyr to the cause of science, contracting psittacosis (parrot fever) in line of duty."

Abstracts from Current Literature

Experimental Pathology and Pathologic Physiology

NOTE ON THE EFFECT OF REPEATED INTRAVASCULAR INJECTIONS OF HEPARIN. W. H. HOWELL and C. H. MCDONALD, Bull. Johns Hopkins Hosp. **46**:365, 1930.

The results indicate that a daily injection of a relatively large dose of purified heparin for six consecutive days does not cause any change in the corpuscles of the blood, nor any significant change in the clotting time. There was certainly no indication of a shortening of this time, but rather a slight tendency toward a lengthening. The excess of heparin injected into the blood was removed, at least in part, through the kidneys.

THYROID HEART, A TRANSITORY CONDITION. HENRY M. THOMAS, JR., Bull. Johns Hopkins Hosp. **47**:1, 1930.

Two similar cases of exophthalmic goiter with severe myocardial insufficiency are reported. In one case, the patient died after operation on the thyroid gland, while in the other the patient achieved complete clinical recovery. This second case, then representing an extreme form of myocardial insufficiency in thyroid heart disease with auricular fibrillation of more than a year's duration, which went on to subsequent complete recovery, demonstrates clearly that even the most severe intoxication from hyperthyroidism need not produce permanent damage of cardiac function. In the first case, as in most others reported in the literature, although death resulted from heart failure, there was no evidence, pathologically, of significant myocardial damage. These cases, coupled with many others from this clinic, as well as from other clinics, place the burden of proof on those who claim that permanent myocardial damage results from hyperthyroidism.

AUTHOR'S SUMMARY.

PHYSIOLOGIC AND CHEMICAL STUDIES FOLLOWING SUCCESSFUL TOTAL GASTRECTOMY FOR CARCINOMA. WALTMAN WALTERS, J. A. M. A. **95**:102, 1930.

In the case presented here, total gastrectomy was performed successfully for an extensive scirrhous carcinoma of the linitis plastica type. Studies made of the chemical changes in the blood, and of the cell count over a period of four months, do not reveal any appreciable change in the number of erythrocytes, in the hemoglobin content, in the carbon dioxide combining power or in the concentration of blood chlorides or urea. Evidence of a definite alkaline tide has not been found. This observation is of interest, since it has been recognized that, with the secretion of gastric juice in a normal person, the urine tends to become more alkaline. The data so far, in this case, appear to indicate that the lack of a stomach and of its acid-secreting glands has a definite effect on the morning alkaline tide.

AUTHOR'S SUMMARY.

VITAL STAINING WITH INDIA INK AND BRILLIANT VITAL RED. J. VICTOR, J. R. VAN BUREN and H. P. SMITH, J. Exper. Med. **51**:531, 1930.

When brilliant vital red is injected into the blood stream of dogs much of it is slowly taken up into numerous phagocytes scattered throughout the tissues ("reticulo-endothelial system" of Aschoff). The rate at which the dye leaves the

blood stream is determined in large part by the action of these phagocytic cells, but the excretion of dye into the bile is also in part responsible for the loss of dye from the plasma. The injection of a small amount of india ink into the blood stream results in lowering the rate at which the dye disappears from circulation. The fact that much of the carbon of the ink is promptly taken up by the phagocytes would lead one to suspect that they were saturated with foreign materials, or "blocked" against the entrance of dye, but it is shown that the ink causes a remarkable inhibition of the excretion of dye into the bile, and this alone seems to account for the longer retention of dye in the blood stream. There is no evidence that any of the retention is due to defective activity on the part of the phagocytes. Thus, prolonged retention of foreign materials in the blood stream cannot be cited to prove "blockade of the reticulo-endothelial system" unless one can rule out such peculiar reactions on the part of excretory organs. It is felt that the literature of "blockade" should be studied with such sources of error in mind.

AUTHORS' SUMMARY.

THE EXPERIMENTAL TRANSMISSION OF LEUKEMIA IN MICE. MAURICE N. RICHTER and E. C. MACDOWELL, J. Exper. Med. **51**:659, 1930.

Lymphatic leukemia has occurred with great frequency in a particular strain of mice which have been inbred by brother-sister matings since 1921. In addition to typical cases of leukemia are others which, because of the absence of leukemic changes in the blood, correspond to "pseudoleukemia" and others which, by the presence of unusually great enlargement of certain lymph node groups, resemble the "leukosarcomatoses" as observed in man. Examinations of the blood of leukemic mice have shown that leukemic blood pictures are not necessarily early in their appearance, nor are they constant. The blood picture may not, therefore, be used as a criterion for the separation of the two diseases (leukemia and pseudoleukemia) but merely indicates different phases of the same condition. Likewise, cases with lesions intermediate between the local growths of "leukosarcomatosis" and the more general lymphatic enlargements of leukemia suggest that these conditions differ only in the distribution of lesions but not in their nature. Lymphatic leukemia occurring spontaneously in this strain may be transmitted to other mice of the same strain, and carried, apparently, for an unlimited number of transfers in animals at an earlier age than that at which leukemia occurs spontaneously. The lesions produced by inoculation correspond to those of spontaneous cases, in that they consist of growths of abnormal lymphoid cells which infiltrate tissues and organs and often appear in the circulating blood. Only minor differences have occurred, some of which are characteristic of certain experimental lines. After repeated transfers, the disease tends to run a more acute course. Among the cases in which transmissions occurred are some without leukemic changes in the blood and many with local growths at the site of inoculation or in certain node groups. The differences in the blood pictures and distribution of lesions (which latter may be influenced to some extent by the method of inoculation) correspond to similar differences which are sometimes observed in the spontaneous cases.

AUTHORS' SUMMARY.

THE GRADIENT OF VASCULAR PERMEABILITY. PEYTON ROUS, H. P. GILDING and FREDERICK SMITH, J. Exper. Med. **51**:807, 1930.

The permeability of the capillaries in the skeletal muscles of mammals increases progressively along their course and is greatest where they pass into the least venules. The gradient of permeability is too largely independent of functional states to give grounds for the view that it is determined by inherent local differences. Through the gradient opportunity is equalized along the capillary. In the liver lobule this object is accomplished by an artifice of arrangement whereby the blood flow past the cells is increased with their distance from the source of

supply. In the urinary bladder the interlacing of capillaries, their progressive widening and a consequent gradual slowing of the blood flow act to achieve the same end. Here a gradient of permeability has not been demonstrable. Where cells of different sorts are served by a slender capillary, their differing requirements may render unnecessary any provision to equalize their opportunities; but where shortcomings in local maintenance will reduce the efficiency of an entire fabric, as the muscle fiber, and where cells of like character live competitively along the same channel, as in the liver, some arrangement must exist to ensure an even distribution of the services rendered by the blood. In situations of the kind last mentioned the immediate environment of the individual cell, the "milieu interne" of Bernard, is not only kept as constant as possible but it must be the same, by and large, for all of the cells. The task of serving voluntary muscle is not strictly limited to the capillaries. The intrafascicular arterioles and venules act so effectively to sustain the tissue about them that where they run no capillaries are supplied.

AUTHORS' SUMMARY.

TOTAL WATER AND CHLORIDE CONTENT OF DEHYDRATED RATS. T. G. H. DRAKE, C. F. MCKHANN and J. L. GAMBLE, J. Exper. Med. **51**:867, 1930.

The circumstances present in upper intestinal obstruction which may be expected to reduce the water content of the body are fasting with water deprivation and a continued loss of secretions into the stomach. According to the data obtained from experiments with rats, loss of body water during the first third of the survival period following pyloric obstruction is more than half accounted for by fasting with water deprivation. This body water is accompanied by a parallel loss of solids and may be regarded as a waste product of the consumption of body fat, glycogen and protoplasm. Its loss does not disturb the percentage of water content of the body tissues. The water lost into the stomach is responsible for an actual excess of water reduction over consumption of solids. Except in the case of the skin and blood, this excess loss of water is extremely small and produces a reduction of the percentage of water content of tissues which is so slight as to permit the surmise that the water loss here derives entirely from the interstitial fluid of the tissues and that no dehydration of tissue cells occurs. The data are, however, not directly informative on this point. The total loss of body water during twelve hours following pyloric obstruction was found to be 12.6 per cent of the water content of a control animal. More than one fourth (28.3 per cent) of the total body content of chloride ion was found to be lost and was entirely accounted for by the amount of chloride found in the gastric contents. Nearly half of the chloride loss occurs from the skin. Data are presented which demonstrate that lower intestinal obstruction causes slight, if any, depletion of the water content of the body.

AUTHORS' SUMMARY.

TOOTH GROWTH IN EXPERIMENTAL SCURVY. GILBERT DALLDORF and CELIA ZALL, J. Exper. Med. **52**:57, 1930.

The incisor teeth of guinea-pigs have a constant rate of growth in health. Deprivation of vitamin C causes the teeth to cease growing. Readministration of the vitamin restores the growth. Administration of small amounts of antiscorbutic substance results in rates of growth roughly proportional to dosage. Under standard experimental conditions used in the testing of foodstuffs for antiscorbutic value, the rate of tooth growth would appear to be a precise indication of the degree of scurvy, being more delicate than the Sherman score, and more constant, as well as more simple, than the Höjer method. Stress in terms of usage appears to exaggerate the scorbutic lesions in the teeth.

AUTHORS' SUMMARY.

Pathologic Anatomy

THE BLOOD CYTOLOGY OF THE RABBIT. LOUISE PEARCE and ALBERT E. CASEY, J. Exper. Med. **52**:23 and 39, 1930.

Observations are reported on the consecutive weekly erythrocyte counts and the hemoglobin contents of the peripheral blood in five groups of normal rabbits, comprising forty-five animals, during a period of twenty months from October, 1927, to July, 1929. The duration of individual group examinations varied from eight to thirty-five weeks. The results are analyzed on the basis of the weekly mean values of each group. On the whole, the erythrocyte values were quite uniform within a narrow range of variation, while the hemoglobin content was comparatively irregular within a wider range of variation. The major changes in the levels of mean values of both the red cells and the hemoglobin, however, were found to be statistically significant. The directions or trends in the levels of the erythrocyte and hemoglobin mean values did not necessarily move in opposite directions. The general levels of the erythrocyte and hemoglobin mean values were not identical for two consecutive years, those of 1927-1928 being higher than those of 1928-1929. The fluctuations of both red cell and hemoglobin mean values observed in one group of animals were also usually observed in another group examined during the same months.

Consecutive weekly observations on the total white cell count of the peripheral blood were made on five groups of normal rabbits, a total of forty-five animals, during a period of twenty months from October, 1927, to July, 1929. The duration of individual group examinations varied from eight to thirty-five weeks. In the case of four groups followed thirteen to thirty-five weeks, the general trend of the total white cell means was toward increasing values; with the group followed eight weeks, the means were maintained at a constant level. The changes in the levels of the granular cell means were usually accompanied by changes in a similar direction of the nongranular cell means. In the case of three of the four groups followed for the longest periods, the greatest relative alterations occurred in the nongranular cells. The fluctuations in the mean values of the total white cells and of the granular and the nongranular cells that were observed in one group of rabbits were also generally observed in another group examined during the same months. The period of greatest irregularity in the mean values of the total white cell means, and of the granular and the nongranular cell means as well, occurred during the late winter and spring months of both years. The general level of the total mean values of the white cells in the groups examined during 1927-1928 was higher than that of the groups observed during 1928-1929. A similar difference was found in the granular and nongranular mean values but it was somewhat less marked in the case of the granular cells.

AUTHORS' SUMMARIES.

THE RELATION OF HEPATITIS TO CHRONIC CHOLECYSTITIS. H. KOSTER, M. A. GOLDZIEHER and W. S. COLLENS, Surg. Gynec. Obst. **50**:959, 1930.

Sections of the liver, taken not less than 8 cm. from diseased gallbladders, in twenty-five of twenty-seven patients, showed chronic inflammatory changes, mainly in the connective tissue about the larger intrahepatic branches of the portal vein. A few nodules of perivascular infiltration were scattered through the liver tissue. The lesion of the gallbladder is regarded as the prior lesion.

RICHARD A. LIFVENDAHL.

SOLITARY TUBERCLE OF THE BLADDER. J. A. BOWEN and G. A. BENNETT, Surg. Gynec. Obst. **50**:1015, 1930.

There was a lesion of the fundus of the urinary bladder characterized by marked thickening as the result of dense white tissue bands extending from the submucosa into the muscularis and the adjacent fat. Microscopically, the structure was typically tuberculous and contained acid-fast rods. The inner surface was extensively ulcerated, and cystoscopically the condition was regarded as carcinomatous.

RICHARD A. LIFVENDAHL.

ARTERIOVENOUS COMMUNICATION BETWEEN RIGHT CORONARY ARTERY AND CORONARY SINUS. B. HALPERT, Heart **15**:129, 1930.

In the body of a man, aged 54, who died from a carcinoma of the stomach, an anastomosis between the right coronary artery and coronary sinus was found. During life, there had been a systolic murmur at the apex of the heart; the blood pressure had been 125 systolic and 70 diastolic. The right coronary artery was 22 cm. long and from 1.5 to 2 cm. in diameter. The anastomosing loop had a structure that was intermediate between an artery and a vein.

GEORGE RUKSTINAT.

PARADOXICAL EMBOLISM. T. THOMPSON and W. EVANS, Quart. J. Med. **23**:135, 1930.

Emboli arising in the systemic venous circulation and lodging in the systemic arterial circulation are known as "paradoxic" or "crossed" emboli. The emboli cross from the venous to the arterial circulation through a patent foramen ovale. The number of recorded cases is not great, and the condition has been recognized only since 1876, when Cohnheim first discovered embolism of the middle cerebral artery arising from the veins of the lower extremities. The authors give a historical review and then classify paradoxic embolism into three groups.

In the first group are those in which thrombosis of the systemic vein is the cause of the embolism; they cite four cases from their own experience, in two of which pulmonary embolism also occurred. It is interesting to note that in one of these cases the patient recovered from cross embolism to the brain.

In the second group are tumor emboli, which are very rare. The authors point out that the possibility of the embolus having traversed the pulmonary circulation before reaching the arterial circulation must be excluded. Thus, they caution that if a growth is present in the lung, even in the presence of a patent foramen ovale, great care must be taken to exclude the possibility of the tumor embolus having traversed the pulmonary circulation. Also, secondary growth deposits in the lung must be excluded by microscopic examination. The suspected tumor embolus should lie free within the lumen of the artery. If it is intimately associated with the wall of the vessel, its formation has probably resulted from the gradual proliferation of tumor cells previously deposited on the intima of the vessel; such observations favor the view that the neoplastic cells have arrived there through the pulmonary circulation. When the embolus is found in the middle cerebral artery, the presence of other deposits in the cerebral cortex suggests that the cells have traversed the pulmonary circulation. When a tumor embolus of the paradoxic type is situated in the cerebral vessels, the clinical notes should contain a history of the sudden onset of a grave symptom such as hemiplegia. When a patent foramen ovale is protected by a valvular fold, the tumor embolus of the paradoxic type can result only following a primary infiltration of the growth along the intra-auricular wall in the right auricle and, finally, its direct extension through the foramen. One authentic case of crossed tumor embolism is reported, the origin of which was in a malignant teratoma of the testicle.

In the third group are the septic emboli; these are the most difficult to account for or to establish as being paradoxic. Because of the facility with which infection passes through the pulmonary circulation, the proof of paradoxic embolism is difficult to establish, even in the presence of an unprotected foramen. It is interesting to note that the foramen ovale is open in about 35 per cent of cases, large enough to admit a small probe in 29 per cent and patent to a pencil in about 6 per cent. The relation between the paradoxic and pulmonary embolus is important since many of the cases are preceded by pulmonary embolism, and the explanation of the subsequent paradoxic embolus is that the blockage in the pulmonary artery raises the intracardiac pressure on the right side; thus the foramen ovale is forced open. Then the second embolus, which reaches the heart, is carried through this foramen, if its size permits. To establish paradoxic embolism by an increase in the pressure in the right auricle, it is necessary that over one third of the pulmonary circulation be obstructed.

N. ENZER.

PERIOSTEAL NEUROFIBROMATOSIS, WITH A SHORT CONSIDERATION OF THE WHOLE SUBJECT OF NEUROFIBROMATOSIS. F. PARKES WEBER, Quart. J. Med. **23**:151, 1930.

The main point in this review is to establish that many of the changes in the bones in neurofibromatosis, if not all, are due to periosteal neurofibromas and not to primary involvement of the bone. Brooks and Lehman, in 1924, studied the changes in the bone in seven cases of neurofibromatosis and showed the presence of neurofibromatous involvement of the periosteum, which seemed in some instances to have penetrated the bone and in all instances to have produced gross changes in the outline of the diseased bone. Weber describes a much thickened and curved tibia in a case of neurofibromatosis in which the periosteal thickening was due to diffuse neurofibromatous infiltration. But he feels that many of the changes in the bone previously reported as being the result or the complication of neurofibromatosis, and generally explained as being the result of elephantiasis, are really secondary to the actual involvement of the periosteum. This periosteal involvement serves as a stimulus to the growth of the bone, and, hence, explains many of the cases of increase in the length of a single long bone.

N. ENZER.

THE MAIN BRANCHES OF THE CORONARY ARTERIES IN ACUTE RHEUMATIC CARDITIS. C. B. PERRY, Quart. J. Med. **23**:241, 1930.

Severe intimal thickening in the main branches of the coronary arteries was discovered in a child, who had suffered from typical anginal pain, and had died during an attack of acute rheumatic fever carditis. This discovery stimulated the author to search for a similar involvement of the coronary artery in other cases of rheumatic fever carditis. Nine hearts were examined from patients, under 20 years of age, who died of acute rheumatic carditis. In all of these, changes were noted in the main branches of the coronary arteries. The changes were patchy thickening of the intima and focal lymphocytic infiltration. The internal elastic layer was irregular, occasionally widely spaced and occasionally condensed. Some intimal proliferation was also noted. In the media, the muscle cells were vacuolated. There was loss of some nuclei and patchy cellular infiltration. The adventitia was thickened, also showing lymphocytic infiltration. Deposits of fat in the wall and in the intima were not found. This emphasizes the widespread involvement of the vascular system in cases of rheumatic fever and emphasizes the importance of a careful search for lesions in the coronary system.

N. ENZER.

CRUVEILHIER-BAUMGARTEN'S SYNDROME (CIRRHOSIS). SERBAN BRATIANO, N. VISINEANO and E. SOLOMON, Ann. d'anat. path. **6**:293, 1929.

From an anatomic point of view, this syndrome is characterized by an enormous splenomegaly, by a chronic lesion of the liver (progressive "functional" atrophy, congenital hypoplasia and cirrhosis) and, what is pathognomonic, by the presence, in the falciform ligament, of a large venous channel leading to a communication between the portal and the parieto-abdominal circulations. This venous channel is regarded as an obliterated and dilated umbilical vein, or possibly a dilated para-umbilical vein. Histologically, the spleen shows changes that are due to stasis.

Clinically, there is a primary splenomegaly and signs of a portal "hypertension" evidenced by the development of an accessory thoraco-abdominal circulation forming enormous unilateral varices. The disease is probably congenital. The authors report a personal observation and give in detail a clinical and pathologic summary of the syndrome.

B. M. FRIED.

TWO CASES OF DIFFUSE PHLEGMONS OF THE STOMACH. D. PETIT-DUTAILLIS, I. BERTRAND, BOPPE and WAITZ, Ann. d'anat. path. **6**:391, 1929.

A report of two cases of phlegmonous gastritis is given in detail. The pathologic process, according to the authors, is always at its maximum at the level of the pylorus. The infiltration stops abruptly at the cardia and the pylorus, never involving the duodenum or the esophagus. The pus infiltrates the submucosa, pushing apart the muscularis mucosae and the muscularis, thus forming a dissecting phlegmon. The mucosa shows edema and a lymphocytic infiltration; the muscularis shows a discrete area of pus. There is a lymphangitis in the subserous membrane where thrombosed vessels are conspicuous. There has been a generalized peritonitis in 70 per cent of the published cases. It is interesting that a diffuse gastric phlegmon may follow a gastrectomy or a gastro-enterostomy.

B. M. FRIED.

A HISTOLOGIC STUDY OF ACUTE CARDIAC RHEUMATISM. H. DARRÉ and G. ALBOT, Ann. d'anat. path. **6**:465, 1929.

The lesion caused by acute rheumatic disease shows nothing characteristic in tissues that are rich in collagen. On the contrary, in areas with a reticular structure and also in those that are rich in lymph spaces, the acute condition tends to form nodular structures resembling those described by Aschoff in the myocardium.

B. M. FRIED.

OCULAR COMPLICATIONS OF PALUDISM. H. VILLARD, Arch. d'opht. **47**:200, 1930.

The conjunctiva is affected in cachectic forms of paludism, becoming dry and wrinkled. In the acute stage of malaria, ulceration and superficial keratitis are seen. Deep keratitis and iritis are more rare. The vitreous may show hemorrhages and exudation. Inflammations of the choroid are not usually seen with the ophthalmoscope, but have been found in eyes examined post mortem. Spasm, hyperemia and hemorrhage of the vessels of the retina and retrobulbar optic neuritis may occur. Optic atrophy is never seen in the early stages of malaria; it is always the outcome of optic neuritis in its grave form. The frontal ramus of the ophthalmic branch of the trigeminal nerve is often affected by neuritis. Severe ocular motor paralyses have also been described in districts in which malaria is endemic and severe.

CHARLES WEISS.

A KNOTTED PULMONARY EMBOLUS. NIPPE, Deutsche Ztschr. f. gerichtl. Med. **15**:330, 1930.

The embolus originated in the right femoral vein following an operation for gangrenous appendicitis. An end of the embolus projected into the right auricle and the unique knot is ascribed to the action of the currents in the auricle.

HIRSCHSPRUNG'S DISEASE. K. OGAWA, Frankfurt. Ztschr. f. Path. **40**:26, 1930.

A case of Hirschsprung's disease is reported. The infant, aged 2 months, had been constipated since birth. Bowel movements were obtained only by the use of enemas. At autopsy, the large intestines were markedly dilated and their walls hypertrophic. The mesentery was of normal length and showed no scar tissue. Histologically, all the elements of the wall of the intestines were hypertrophic, with the exception of the nervous elements, in particular the plexus of Auerbach. The author assumes that the marked meteorism of this case was due to the fact that the peristalsis, even though of normal intensity, was too weak for the markedly hypertrophic colon. The belief is expressed that cases of megacolon which show neither meteorism nor any other clinical signs of Hirschsprung's disease reveal, in addition to hypertrophy of the muscle fibers of the intestine, abnormally large nervous elements in the intestinal wall. The peristaltic wave, therefore, might be more powerful, lead to normal bowel movements and prevent the appearance of the clinical symptoms of Hirschsprung's disease.

ARTERIOSCLEROSIS IN THE PARROT. G. PALLASKE, Frankfurt. Ztschr. f. Path. **40**:64, 1930.

The arteriosclerotic changes in two parrots, about 30 and 40 years old, are described. The conclusion is reached that arteriosclerotic lesions in the parrot correspond with arteriosclerotic changes in man, but not with those in the dog and the horse.

HODGKIN'S DISEASE COMBINED WITH ACUTE MYELOID LEUKEMIA. M. A. SKWORZOFF, Frankfurt. Ztschr. f. Path. **40**:81, 1930.

The lymph nodes in a girl, aged 8, especially those in the region of the neck, were markedly enlarged and showed changes typical of Hodgkin's disease. Dorothy Reed cells and many eosinophils were encountered. A fibrous replacement of the lymph nodes was also noted. In addition, there were many polymorphonuclear leukocytes, myelocytes and myeloblasts. The latter gave a positive oxydase reaction. The spleen and bone-marrow were the seat of myeloid metaplasia. Accumutions of myeloid cells were present in the liver, suprarenal glands, uterus, ovaries, urinary bladder and kidneys. Chemical examination of the blood showed 360,000 white cells; the differential count revealed: myeloblasts, 85.5 per cent; promyelocytes, 2 per cent; myelocytes, 1.5 per cent; metamyelocytes, 3 per cent; neutrophils, 4 per cent; lymphocytes, 2 per cent; monocytes, 0.5 per cent, and eosinophils, 1.5 per cent; thus the blood picture was characteristic of myelogenous leukemia. A gangrenous process of the pharynx aided in making the diagnosis. The question is discussed whether this case presents a true myelogenous leukemia superimposed on a primary Hodgkin's disease, or whether this is a case of a leukemia-like reaction of the organism against the unknown virus of Hodgkin's disease.

ENCEPHALITIS IN EXSICCOSIS. M. A. GOLDZIEHER, Klin. Wchnschr. **9**:981, 1930.

A proliferative process in the midbrain is described which is regarded as having significance in water metabolism.

CHARACTERISTICS OF BILIRUBIN IN ICTERUS NEONATORUM. L. ASCHOFF and R. HUMMEL, Virchows Arch. f. path. Anat. **275**:1, 1930.

In the opening article of a volume of *Virchows Archiv* issued as a Festschrift to its editor, Lubarsch, on the occasion of his seventieth birthday, Aschoff and Hummel discuss some of the peculiarities of bilirubin in icterus neonatorum. In agreement with most modern writers, they hold that icterus neonatorum is a physiologic process that is to be distinguished from pathologic icterus of the newborn or icterus neonatorum. One of the most striking characteristics of the physiologic jaundice is the crystallization of bilirubin in the living condition, a phenomenon to which Orth called attention more than fifty years ago. According to the present writers, this phenomenon does not occur in the jaundice of later life except in the rarest instances, and then only in the form of icterus that Aschoff has termed hyperfunctional and not in the obstructive type. In icterus neonatorum, crystallization of bilirubin is seen not only in the blood, but also in the tissues, especially within fat cells, and in the fluid of the serous cavities. Crystallization was noted most frequently, and the content of bilirubin was highest in the pericardial cavity, next in the peritoneal cavity, then in the subdural space and least in the pleural cavities. This variation in the content of the bilirubin in the serous fluids is directly proportional to the richness of the lining serous membrane in histiocytes. The crystals of bilirubin seen in the fluids were usually within free histiocytes. In premature infants, in stillborn fetuses and in new-born infants immediately after birth, the blood, the serous fluids that contain bilirubin, the bile of the gallbladder and the meconium give only the indirect van den Bergh reaction. The direct van den Bergh reaction, which Aschoff previously ascribed to bilirubin that has passed the liver cell, does not appear until the liver function has been established. Deposits of biliary pigment were not seen

in the urine of icteric new-born infants. The kidney does not appear to be able to excrete the form of bilirubin that is present in icterus neonatorum, and the tubular bilirubin infarcts sometimes seen in the kidneys of these infants are not due to excretion of the pigment. The peculiar characteristics of the bilirubin of icterus neonatorum are interpreted as evidence of excessive extrahepatic formation of bilirubin in the fetus and in the new-born infant.

O. T. SCHULTZ.

THE ALVEOLAR PHAGOCYTES OF THE LUNG. F. J. LANG, Virchows Arch. f. path. Anat. **275**:104, 1930.

In a previously reported work on tissue culture of the lung, Lang reached the conclusion that the phagocytic cells of the lung alveoli are mesenchymal in origin and are not alveolar epithelia. In the present article, he briefly summarizes his work and that of others that upholds this conclusion. The article includes material on the embryologic investigations of Policard, Ogawa, and Chiodi, his own work on tissue culture, the morphology of the cells and their presence within the septums, the results of the application of the supravital staining technic by Gardner and Smith and by Foot, a description of the ability of the cells to phagocytose bacteria and particulate matter and the storage of lipoid by the cells in lipoid histiocytosis, as reported by Bloom. All these facts, according to Lang, establish beyond question the nonepithelial character of the alveolar phagocytes, or septum cells, as he prefers to term them. The cells are the derivatives of the system of slumbering mesenchymal cells that retain their embryonic potencies of being awakened into activity under a variety of stimuli. In the lung, their function is the cleansing of the lung of foreign particles that reach the normal lung tissue, and the protection of the lung in disease by the ingestion of bacteria, particulate material and colloid substances that reach the lung from without or by way of the blood stream.

O. T. SCHULTZ.

BASOPHIL CELLS OF THE HYPOPHYSIS AND CHRONIC RENAL DISEASE. W. BERBLINGER, Virchows Arch. f. path. Anat. **275**:230, 1930.

Berblinger investigated variations in the content of basophil cells in cases of adenohypophysis in a series of seventy-one adults of both sexes without renal disease, and in a series of seventy-one adults of both sexes with chronic renal disease. In the group without renal disease, the basophil cells were increased above what Berblinger considered the normal average in 28 per cent, and decreased in 11 per cent. In the group with renal disease, the number of basophil cells was increased in 67 per cent, and decreased in 3 per cent. The numerical variations bore no relation to the age or to the constitutional type. Berblinger concluded that the frequency with which the basophil cells are increased in number in cases of renal disease indicates a relationship between this type of cell, the blood pressure and the renal function.

O. T. SCHULTZ.

MULTINUCLEATED SPERMATIDS IN THE TESTIS. W. DI BIASI, Virchows Arch. f. path. Anat. **275**:250, 1930.

Multinucleated spermatids were seen in the testes of 27 per cent of 165 cases examined. In a series of 80 cases more carefully examined, they were detected in 58 per cent. They are about the size of spermatocytes, but may appear as multinucleated giant cells. They are formed by fusion, although repeated nuclear division without division of the cells cannot be excluded as a mode of formation. They were seen at all ages after puberty. They occur in testes that have been only slightly damaged by the general state of the person, and are probably also a constituent of the normal testis.

O. T. SCHULTZ.

BONE-MARROW OF THE FEMUR. T. FAHR, Virchows Arch. f. path. Anat. **275**: 288, 1930.

Fahr presents a study of the bone-marrow of the femur, based on 500 necropsies in which the entire femur was removed and the marrow examined. The age in 13 cases, including those for control and for comparison, was under 18 years. Fahr agrees with Askanazy, Hedinger and Neumann in their assertion that the usual statement in textbooks that the normal marrow of the long bones in adults is entirely fatty is incorrect. In his series, an adipose marrow, which sometimes contained a few small islands of red marrow at the upper end of the diaphysis, was seen in only 14 per cent. In 60 cases of tuberculosis, the marrow was wholly fatty in only 3 per cent, considerably under the average for the group. In syphilis, the marrow was fatty in 38 per cent, a figure much above the average for the group, and in infectious diseases other than tuberculosis or syphilis, the figure was 16 per cent. Contrary to the opinion of Schridde, mucoid degeneration of the marrow was not associated with increasing age, but it was encountered more frequently in persons under 50 years of age than in those above this age. It was seen in 12 per cent of the cases of tuberculosis, as compared with 8 per cent for the rest of the series. A practically complete replacement of adipose by red marrow was noted in 7 per cent of the 487 persons over 18 years of age. Such complete replacement was seen in 24 per cent of 55 cases of tuberculosis in persons over 18 years of age, as compared with 5 per cent for the rest of the group. Replacement of adipose by red marrow in cases of tuberculosis may be as marked as in pernicious anemia. The change is not due to actual tuberculous involvement of the marrow, but to a disturbance of leukopoiesis. The nature or cause of this disturbance is not discussed. That there is also slight disturbance of erythropoiesis in tuberculosis is evidenced by the presence of iron pigment in the Kupffer cells of the liver. Fahr presents tabulations of the distribution of iron in the liver, spleen and celiac lymph nodes in tuberculosis and pernicious anemia.

O. T. SCHULTZ.

THE CYTOLOGY OF THE CONJUNCTIVA IN TRACHOMA AND THE PROBLEM OF ITS PATHOGENESIS. P. P. DWIJKOFF and E. F. LEUKOEWU, Ztschr. f. Augenh. **71**:314, 1930.

In trachoma, the cytology of the material obtained by expression of follicles and scrapings of the conjunctiva is characteristic of the disease and is related to the clinical picture. In stage 1, the lymphoid type of cells predominate, especially the small lymphocytes. The most characteristic and pathognomonic cells seen are the lymphoblasts. Plasma cells are rarely seen, and there are few polymorphonuclears or eosinophils. Epithelial cells are present in large masses. In stage 2 there is a general increase in all of the cells, particularly in the large lymphocytes and lymphoblasts. There is also a slight increase in the plasma cells. Nucleated red cells now make their appearance. Stage 3 is characterized by a decrease in the lymphoblasts, lymphocytes and plasma cells. This picture is not seen in allied diseases of the conjunctiva, such as follicular, hyperplastic, swimming pool and Parinaud's conjunctivitis, or in tuberculosis.

The authors emphasize the point that the cells of the trachomatous follicle, which writers (Löhlein, and others) have called epithelioid, are really lymphoblasts. They agree with Pascheff that the conjunctiva is a blood-forming, lymphatic apparatus, and conclude that the proliferation of young cells of the lymphoid series, especially lymphoblasts, and the absence of morphologic signs of inflammation support the idea that trachoma is not an inflammatory but a hyperplastic process similar to leukemia.

CHARLES WEISS.

Microbiology and Parasitology

RECURRENT AGRANULOCYTOSIS. B. H. RUTLEDGE, O. C. HANSEN-PRUSS and W. S. THAYER, Bull. Johns Hopkins Hosp. **46**:369, 1930.

We are presenting a remarkable instance of cyclic, agranulocytic angina associated with fever and constitutional symptoms but without anemia, beginning at the age of 2½ months and recurring at intervals of approximately three weeks, during the entire life of a man 20 years of age. While apparently unique in medical literature, the picture is so sharply defined and clear that we are inclined to think that it represents a definite complex of symptoms which may be less infrequent than one might fancy at the moment. For this reason, we desire to place the history on record.

AUTHORS' SUMMARY.

THE HYDROLYSIS OF SODIUM HIPPURATE BY VARIOUS BACTERIA. ISABELLE GILBERT and MARTIN FROBISHER, JR., Bull. Johns Hopkins Hosp. **47**:55, 1930.

Except *Bacillus aerogenes* and *B. bronchisepticus*, the gram-negative, aerobic, nonspore-forming rods studied were without action on sodium hippurate. Staphylococci generally split up the hippurate, but the power varies in different strains. The results indicate that the test will be of value.

THE UPPER RESPIRATORY FLORA OF INFANTS. YALE KNEELAND, JR., J. Exper. Med. **51**:617, 1930.

The upper respiratory tract is sterile at birth. In the first two weeks of life the infant acquires a basal flora comparable to that of adults except that the potential pathogens are absent. During the ensuing months the potential pathogens may appear without giving rise to symptoms and by eight months the infant's flora is entirely comparable to the adult's. There is no evidence of a specific bacterial incitant for the first colds of infancy. In infants with recurrent colds, secondary infection of the nose with pneumococci or *B. pfeifferi* probably plays a part.

AUTHOR'S SUMMARY.

THE TRANSMISSION OF YELLOW FEVER. NELSON C. DAVIS, J. Exper. Med. **51**:703, 1930.

Saimiri sciureus has been infected with yellow fever virus, both by the inoculation of infectious blood and by the bites of infective mosquitoes. Some of the monkeys have died, showing lesions, including hepatic necrosis, suggesting yellow fever as seen in human beings and in rhesus monkeys. Virus has been transferred back to *M. rhesus* from infected *Saimiri* both by blood inoculation and by mosquito bites. The virus undoubtedly has been maintained through four direct passages in *Saimiri*. Reinoculations of infectious material into recovered monkeys have not given rise to invasion of the blood stream by virus. Serums from recovered animals have protected *M. rhesus* against the inoculation of virus. It has been possible to pass the virus to and from *Ateleus ater* by the injection of blood or liver and by the bites of mosquitoes. The livers from two infected animals have shown no necrosis. The serum from one recovered monkey proved to be protective for *M. rhesus*. Only three of twelve *Lagothrix lagotricha* have reacted to yellow fever virus by a rise in temperature. Probably none has died as a result of the infection. In only one instance has the virus been transferred back to *M. rhesus*. The serums of recovered animals have had a protective action against yellow fever virus.

AUTHOR'S SUMMARY.

EXPERIMENTAL EPIDEMIOLOGY OF TUBERCULOSIS. MAX B. LURIE, J. Exper. Med. **51**:729, 743, 753 and 769, 1930.

If normal guinea-pigs are confined with an equal number of tuberculous cage mates the incidence of "contact" tuberculosis is increased by crowding. This is

probably due largely to an increase in the amount of tubercle bacilli available in the more crowded cages, although no constant relationship could be established between the intensity of the exposure and the incidence of tuberculosis acquired by contagion. Other factors must be determined. If guinea-pigs are inoculated intraperitoneally with a given quantity of human tubercle bacilli and distributed in different degrees of crowding, the duration of survival is shortened in the more crowded animals and the incidence of chronic types of tuberculosis is greater among the less crowded animals.

Guinea-pigs living in the same room but not in the same cage with tuberculous animals acquire tuberculosis, characterized by a chronic course, a marked involvement of the lungs, often with cavity formation, and a massive tuberculosis of the tracheobronchial nodes; the mesenteric and cervical nodes are slightly or not at all affected. The route of infection in these guinea-pigs is almost always the respiratory tract. Of 103 guinea-pigs exposed for a period of up to thirty-two months 15, or 14.5 per cent, developed tuberculosis. The shortest period of exposure leading to fatal tuberculosis was eight months. The incidence of this tuberculosis acquired by air-borne contagion increases with the duration and intensity of the exposure up to a certain point. A large percentage of the guinea-pigs weathered a continuous exposure to the tubercle bacillus for thirty-two months without becoming tuberculous. This may be due to an innate natural resistance against tuberculosis, or to an acquired immunity resulting from the continuous exposure to the contagion.

If normal guinea-pigs are confined with tuberculous cage mates in cages where the food becomes contaminated with the excreta, laden with tubercle bacilli, of the inoculated animals, the incidence of acquired tuberculosis among them is greater than among guinea-pigs similarly exposed in cages where this mode of infection is largely eliminated. The disease acquired in the first type of cage is largely of enteric origin and is chronic in type. The disease acquired in the second type of cage is of respiratory origin and has a more acute course.

In tuberculosis of guinea-pigs acquired by contact with tuberculous guinea-pigs under conditions permitting the entrance of tubercle bacilli by way of both the alimentary and the respiratory tracts, the type of lesion produced depends on the relative intensity of exposure to infection by one or the other channels. With the gradual elimination of exposure to alimentary infection tuberculosis is more and more completely engrafted through the respiratory route. With the gradual increase in the intensity of exposure to alimentary infection, the disease becomes more and more completely enteric in origin. Some evidence is presented that the engrafting of tuberculosis by way of the alimentary route inhibits the development of respiratory disease.

AUTHOR'S SUMMARIES.

EXPERIMENTS WITH THE VIRUS OF POLIOMYELITIS. RICHARD THOMPSON, J. Exper. Med. **51**:777, 1930.

Efforts to adapt the virus of poliomyelitis to the rabbit organism and to produce poliomyelitis in rabbits by testicular injection and by cerebral injection after testicular passage produced no evidence that the virus could be adapted in this manner. Suggestive symptoms produced in very young rabbits were duplicated in nonspecifically treated and in uninoculated controls. The admixture of a vaccine virus, adapted to the rabbit organism, with the poliomyelitis virus in similar injections and passages did not aid the adaptation. The virus of poliomyelitis did not survive twenty-four hours in the rabbit testicle — whether alone or mixed with vaccine virus. Repeated intraperitoneal and intradermal injection of poliomyelitis virus and of poliomyelitis and vaccinia virus mixtures produced no disease in rabbits. Massive doses of concentrated virus by stomach tube in conjunction with meningeal irritation produced no symptoms in rabbits. No neutralizing substances against poliomyelitis virus could be produced in rabbits by the repeated intraperitoneal and intradermal injection of poliomyelitis virus or of poliomyelitis-vaccinia virus mixtures. Although attempts to infect monkeys by intrastomachic injections, after

bile irritation of the mucosa, were entirely negative, evidence was obtained that repeated intrastomachic injection after bile irritation may produce an appreciable degree of immunity. No evidence could be obtained that the cellular elements of the blood contain the virus in any greater proportion than the whole blood. One attempt to immunize by neutral virus-serum mixtures was entirely negative.

AUTHOR'S SUMMARY.

METHODS FOR THE PURE CULTURE OF CERTAIN PROTOZOA. R. W. GLASER and N. A. CORIA, J. Exper. Med. **51**:787, 1930.

Some mediums are described which inhibit bacterial growth, but are favorable to protozoan development. A purification technic, which takes advantage of geotropic responses, was devised and used successfully with seven species of protozoa, including flagellates and ciliates. The method was also used with *Spirillum*. For one flagellate which could not be purified in this manner, a procedure involving chemical sterilization was employed. *Paramecium caudatum* was purified, but failed to develop subsequently in the absence of living micro-organisms. Four of the protozoa which were purified ingest other micro-organisms normally. The work shows that purified protozoa grow well under proper conditions, and then they can be studied culturally and biologically, like bacteria.

AUTHORS' SUMMARY.

DISSOCIATION OF THE TUBERCLE BACILLUS. S. A. PETROFF and WILLIAM STEENKEN, JR., J. Exper. Med. **51**:831, 1930.

Petroff and Steenken, in studying the colony formation of the tubercle bacillus, found evidences of dissociation similar to that of other organisms. They distinguish several types of colonies but have studied only the two extreme types, the "R" and "S." They use the term 'R" to indicate greater resistance to environment and relative avirulence, and "S" to indicate greater sensitiveness to environment and more virulence to certain species. The terms rough and smooth can be applied only to the avian bacillus when grown on plain gentian violet-egg medium. The addition of 0.25 per cent of sodium taurocholate to this brings out the "R" and "S" types. The human tubercle bacillus has been dissociated with great difficulty, and the study is not yet complete. The "R" and "S" types have been obtained from four B C G cultures; this work has been reported elsewhere. The authors believe that each organism has two components, "R" and "S." If the environment is favorable, "R" may change to "S," or vice versa.

L. E. COOLEY.

STUDIES ON MEXICAN TYPHUS FEVER. HANS ZINSSER and ALBERT P. BATCHELDER, J. Exper. Med. **51**:847, 1930.

The authors reinvestigated some of the fundamental problems of Mexican typhus fever. They found that the virus is not filtrable. The results of the filtration experiments suggest that the virus is comparable in magnitude to the tunica bodies observed by Mooser. The virus is firmly associated with red blood cells, but hardly at all with leukocytes. The virus remains alive in tunica material and in glass capsules within the peritoneum of guinea-pigs for about ten days. They failed to keep the virus living except in the presence of living cells. Tunica material containing Mooser bodies (probably *Rickettsia*) is more virulent than blood plasma. The authors believe that the tunica lesions in guinea-pigs are an integral part of the disease. Convalescent blood and virus mixed in a test tube afford protection if the blood is taken between the first and tenth days after defervescence. Several guinea-pigs developed an active immunity by this method. No complement-fixation bodies were found. There was suggestive evidence of an active immunization with tunica material in formaldehyde. The authors believe that the small giemsa-staining bodies observed by Mooser in the tunica of guinea-pigs with Mexican typhus represent the virus of the disease.

L. E. COOLEY.

CENTRIFUGE EXPERIMENTS WITH THE VIRUS OF VACCINIA. F. F. TANG, J. Exper. Med. **51**:859, 1930.

Centrifuge experiments have been carried out with cell-free, active filtrates of vaccinia virus. The experiments have shown that the virus can be concentrated by this method, even in filtrates which have been subjected to prolonged preliminary centrifugalization to throw down any inert particles which may have been present in the original filtrate. This fact, together with the knowledge that the virus can be almost completely held back by the Berkefeld N filter, as reported previously, indicates that the virus may be of considerable size.

AUTHOR'S SUMMARY.

CULTIVATION AND CLASSIFICATION OF "BACTEROIDES," "SYMBIONTS," OR "RICKETTSIAE" OF BLATTELLA GERMANICA. R. W. GLASER, J. Exper. Med. **51**:903, 1930.

In *Blattella germanica,* the German roach or "croton bug," bacteriocytes are found in all individuals of both sexes. These bacteriocytes are scattered throughout the fat tissue and their cytoplasm is filled with micro-organisms. Evidence is presented to show that the intracellular parasites are diphtheroidal bacilli. These diphtheroids are transmitted from one generation to another through the ova. By using a technic previously described, the intracellular parasites were isolated and cultivated from the adult bacteriocytes and from embryos. Two diphtheroidal strains were cultivated with approximately equal frequency. These two strains resemble one another closely enough to be considered a single species but show certain minor differences. The size, general morphology and tinctorial reactions of the two cultures correspond to the intracellular parasites of *Blattella germanica.* They may be distinguished from the three types of *Corynebacterium periplanetae* variety *americana,* previously described. For the species here discussed the name *Corynebacterium blattellae,* nov. sp., is proposed.

AUTHOR'S SUMMARY.

THE EPIDEMIOLOGY OF SPECIFIC INFECTIOUS CYSTITIS AND PYELONEPHRITIS OF COWS. F. S. JONES and RALPH B. LITTLE, J. Exper. Med. **51**:909, 1930.

Bacteriologic examination of the genito-urinary tract of calves originating in a herd in which infectious cystitis and pyelonephritis existed among the cows revealed a variety of cultural types of diphtheroids. Of these types, one obtained from a considerable number of the calves resembled in morphology and cultural characteristics the organism cultivated from the actual cases of the disease. This group had agglutination affinities like those of the organism mentioned and was capable of absorbing agglutinin from antiserum specific for it. When three cows were inoculated intra-urethrally with cultures isolated from the sheaths of calves, two developed transient infections and the other a severe prolonged cystitis and pyelonephritis.

AUTHORS' SUMMARY.

THE EFFECT OF CATHODE RAYS UPON CERTAIN BACTERIA. RALPH W. G. WYCKOFF and THOMAS M. RIVERS, J. Exper. Med. **51**:921, 1930.

For the two motile bacilli, *B. coli* and *B. aertryke,* the absorption of a single 155 kilovolt electron is sufficient to cause death. Furthermore, all, or nearly all, the electrons absorbed are lethal. The same is undoubtedly true of *Staphylococcus aureus.* In addition to providing a quantitative picture of the interaction of bacteria and cathode rays, these results suggest that radiation of the energy content used in our experiments is not suitable for altering the inheritable characteristics of bacteria. The differences in sensitivity to cathode rays shown by the bacteria studied can be explained by the purely physical factor of size. Counts giving significant conclusions concerning killing rates can be obtained only if there is no clumping of the cells when spread and only if the cells are not allowed to

multiply before irradiation. Both these precautions seem rarely to have been met in the experiments with roentgen rays and with other forms of radiation that have been made in the past.

AUTHORS' SUMMARY.

RISE IN TEMPERATURE PRECEDING THE SYMPTOMS IN EXPERIMENTAL POLIOMYELITIS. S. D. KRAMER, K. H. HENDRIE and W. L. AYCOCK, J. Exper. Med. **51**:933, 1930.

The data presented in this paper offer a means of earlier recognition of experimental poliomyelitis in the monkey. The early appearance of the temperature rise (one to three days before the onset of the usual recognizable symptoms) associated with spinal fluid changes suggests that there is a stage in the experimental disease corresponding to preparalytic human poliomyelitis.

AUTHORS' SUMMARY.

INFECTIOUS MYXOMATOSIS OF RABBITS. T. M. RIVERS, J. Exper. Med. **51**:965, 1930.

The virus of infectious myxomatosis of rabbits (*Sanarelli*) induces multiple lesions in the skin, lymph glands, tunica vaginalis, epididymis, testicle, spleen and lungs. Growth and destruction of cells in the epidermis overlying the myxomatous masses lead to the formation of vesicles. Cytoplasmic inclusions are found in affected epidermal cells. Occasionally, similar inclusions are seen in other involved epithelial cells. The nature of the inclusions is an open question. In the myxomatous masses situated in the subcutaneous and other tissues, evidences of alteration and growth of certain cells are observed.

AUTHOR'S SUMMARY.

THE SURVIVAL OF YELLOW FEVER VIRUS IN CULTURES. PAUL A. LEWIS, J. Exper. Med. **52**:113, 1930.

The virus of yellow fever has been found to survive in artificial culture mediums for at least twelve days at a temperature of 35 C. No visible growth has been present and no reproduction of the virus has been demonstrated. Infections have been obtained in rhesus monkeys with two strains of virus in quantities as small as 0.00001 cc. of infectious blood, and with one strain in an amount probably as minute as 0.000001 cc.

AUTHOR'S SUMMARY.

BARTONELLA MURIS ANEMIA IN ALBINO RATS. J. MARMORSTON-GOTTESMAN and DAVID PERLA, J. Exper. Med. **52**:121 and 131, 1930.

The virus of *Bartonella muris* anemia of splenectomized rats may be transmitted to normal young unoperated rats and rabbits. This confirms the observations of Ford and Eliot. *Trypanosoma lewisi* infections in normal adult rats are accompanied by an anemia most marked at the height of the infection and the appearance of *Bartonella muris* bodies in the red blood cells. In young rats *Trypanosoma lewisi* may produce death from the severity of the anemia, complicating the disease. The anemic virus may be separated from *Trypanosoma lewisi* infected blood by passage through young rabbits with subsequent maintenance of the strain in immature rats. A strain of the virus of *Bartonella muris* anemia capable of producing anemia in young rabbits and young rats for successive transfers has been isolated from the blood of normal adult unoperated rats by passage through young rabbits. The adult normal rat is a carrier of the *Bartonella muris* virus. Splenectomy in young suckling rats separated from the mother is not followed by a *Bartonella muris* anemia. The young suckling rat is not a carrier of the infection.

Autoplastic splenic transplants were made in adult albino rats four and seven weeks prior to splenectomy and the protective effects against infection with the *Bartonella muris* anemia observed. One fourth of the spleen left in situ will protect adult albino rats against *Bartonella muris* anemia. Autotransplantation of splenic

tissue in adult rats is successful in over 90 per cent of instances. Autoplastic splenic transplants performed seven weeks prior to splenectomy afford protection against *Bartonella muris* anemia in more than 50 per cent of instances, whereas four week old transplants do not protect. A comparative histologic study of the transplants of protected and unprotected rats reveals a regeneration of the pulp cells in the protected rats and an exhaustion destruction of the pulp in the unprotected rats. The reticular cells play a specific rôle in protecting the adult albino rat against *Bartonella muris* anemia.

AUTHORS' SUMMARIES.

FURTHER NOTES ON THE CULTURE OF THE NITROSO-BACTERIUM. H. S. FREMLIN, J. Hyg. **29**:236, 1929.

The nitrosobacterium inoculated into sterile urine does not produce nitrites. If, however, urine is added to an active culture of this micro-organism, nitrites are rapidly developed.

A nitrosobacterium culture developed in bulk in peat and chalk can be used as a urinal. After passing through this urinal, all ammonia in urine appears to have been converted into ammonium nitrite and nitrate. No odor is noticeable when this urine is left to evaporate at either 37 C. or at room temperature.

Urine rendered ammoniacal before use and then sterilized is also a good medium for the growth of the nitrosobacterium.

The nitrosobacterium is difficult to isolate because (1) when colonies are developed on a dilution plate sufficiently spaced to allow of certainty in subculture, nitrification only rarely takes place in the subculture, and when it does take place some months are required for the production of a measurable amount of nitrite, and because (2) the nitrosobacterium usually grows in association with some other, more rapidly growing species. The colonies of this other micro-organism often appear to be pure, but when growth has proceeded for some days individual colonies of the nitrosobacterium may appear in a certain percentage of the plates.

AUTHOR'S SUMMARY.

AN EPIDEMIOLOGICAL STUDY OF DIPHTHERIA IN A REMOTE NEW ZEALAND COMMUNITY. C. E. HERCUS, R. A. SHORE, H. E. BARRETT and J. H. NORTH, J. Hyg. **29**:243, 1929.

The epidemiologic and immunologic studies of two outbreaks of diphtheria occurring in a remote and unsettled country district in New Zealand are presented. The first epidemic occurred in August and was thought to be air borne. This was followed in the succeeding spring by the second epidemic, which was probably milk borne.

"The practical lessons which may be learnt from this study are: (a) That unless a special buffered diluent is used, the toxin used for Schick testing must be freshly diluted near the place where it is to be used. (b) Active immunization of remote, unsettled communities against diphtheria requires more time, and more intensive courses of prophylactic, than areas where diphtheria has been endemic for some years. (c) In such places with a low original herd immunity, it is essential, even more than in endemic centers, never to omit retesting those who have been inoculated, in order to be certain that any attempt made to induce active immunity to diphtheria may be successful. (d) Estimations of the relative efficiency of diphtheria prophylactics, which are based on the rapidity with which samples of children become immune, are worthless unless all the observations have been made in the same environment on groups having the same original herd immunity. (e) An immunity, good enough to withstand droplet infection in a day school environment may be broken down by massive doses of diphtheria bacilli in milk."

J. N. PATTERSON.

PARATYPHOID C, AN ENDEMIC DISEASE IN BRITISH GUIANA. GEORGE GIGLIOLI, J. Hyg. **29**:273, 1929.

From seventy-two cases of pyrexial illness occurring in British Guiana, an organism has been isolated which has the cultural and serologic reactions of *Bacillus paratyphosus C* (Hirschfeld). It seems probable that enteric fever due to infection with this organism is now endemic in the colony and is an important cause of sickness and death.

AUTHOR'S SUMMARY.

NOTE ON THE CULTIVATION OF AN ACID-FAST BACILLUS FROM LEPROSY. W. B. WHERRY, J. Infect. Dis. **46**:263, 1930.

In an attempt to cultivate the bacillus in leprosy, special attention was given to the oxygen and carbon dioxide supply under both aerobic and anaerobic conditions. The medium used consisted of a glycerinated ovomucoid yolk solution added to agar. The best growth was obtained in two tubes kept for a month at partial oxygen tension (little oxygen but carbon dioxide present), after which the tubes were kept under oxygen and carbon dioxide. The rods in the cultures were thinner than tubercle bacilli, and when Löffler's blue was used as a contrast stain they frequently were found to contain one or two blue granules.

THE BEHAVIOR OF ESCHERICHIA COLI AND ITS SPECIFIC BACTERIOPHAGE IN URINE. FRANCES C. FRISBEE and WARD J. MACNEAL, J. Infect. Dis. **46**:405. 1930.

The colon bacillus grows more actively in human urine when the latter is slightly acid in reaction rather than alkaline.

The bacteriophage actively lytic for the colon bacillus is most effective against this organism in urine culture when the reaction of the latter is acid, with p_H of from 5.6 to 6.3.

The bacteriophage is not unfavorably influenced by exclusion of air from the cultures in urine.

The urinary antiseptics, formaldehyde and acriflavine, are distinctly unfavorable to the action of the bacteriophage, in concentrations too weak to exert an appreciable effect on the growth of the colon bacillus in urine.

AUTHORS' SUMMARY.

BRUCELLA ABORTUS IN CERTIFIED MILK. D. E. HASLEY, J. Infect. Dis. **46**:430, 1930.

The results of this investigation show that it is possible to detect *Brucella abortus* in market certified milk by plating methods. *B. abortus* was grown from 10 to 230 samples examined. The 10 positive samples were obtained from 3 of the 5 dairies studied. The highest number of organisms found was 8 per cubic centimeter of milk; the average for the 10 positive samples was 2 per cubic centimeter.

AUTHOR'S SUMMARY.

BACTERIOLOGY OF THE BLOOD IN CHRONIC INFECTIOUS ARTHRITIS. HARRY M. MARGOLIS and ANNA H. E. DORSEY, J. Infect. Dis. **46**:442, 1930.

In several cases of a large series studied, nonhemolytic streptococci were isolated from the blood of patients with chronic infectious arthritis. These streptococci were identical morphologically and culturally with those isolated by us previously from the joint tissues of patients with chronic arthritis.

The infrequency of positive blood cultures in our series as compared with that of Cecil, Nicholls and Stainsby lacks definite explanation. The factors that possibly account for this discrepancy may be extended treatment of the patient before the time of making cultures, the season of the year in which the cultures were taken

and, most important of all, the inconstancy of the bacteria in the blood of patients with arthritis and the small number of organisms circulating in the blood when bacteremia occurs in arthritis.

The occurrence of the organisms in the blood, as well as in the joints of patients with arthritis, suggests that these bacteria are of etiologic significance in this disease.

AUTHORS' SUMMARY.

LESIONS PRODUCED IN RABBITS BY CULTURES OF MICROCOCCUS GAZOGENES (LEWKOWICZ). BEATRICE F. HOWITT, J. Infect. Dis. **46**:491, 1930.

Lesions of the joints or pyogenic abscesses may be produced in rabbits by intravenous or intraperitoneal inoculations of the mouth organism, *M. gazogenes* (Lewkowicz), a small, gram-negative, gas-producing anaerobe.

AUTHOR'S SUMMARY.

DIFFERENTIAL ACTION OF OXIDIZING AGENTS ON CERTAIN GRAM-POSITIVE AND GRAM-NEGATIVE ORGANISMS. ESTHER WAGNER STEARN and ALLEN E. STEARN, J. Infect. Dis. **46**:500, 1930.

More than fifty strains of organisms were subjected to various oxidizing environments and their relative susceptibilities tested.

A few strains were subjected in the same way to one reducing environment.

In general, the gram-negative organisms are more susceptible to an oxidation-reduction environment differing from that of ordinary broth than the gram-positive. This is shown to be true when the oxidation potential is higher, and is indicated in a preliminary way in one case in which the potential is lower, than that of ordinary broth.

These results are discussed from the point of view of recent ideas on oxidation-reduction environment.

AUTHORS' SUMMARY.

THE ABSENCE OF SEASONAL CHANGE IN THE TOXIN-PRODUCING CAPACITY OF THE DIPHTHERIA BACILLUS. ARTHUR LOCKE and E. R. MAIN, J. Infect. Dis. **46**:514, 1930.

The toxin production of the Park 8 strain of the diphtheria bacillus has been observed, under controlled conditions, for one year. At no time during that interval was there any indication of a significant seasonal fluctuation in the amount of toxin produced.

The seasonal variations in yield occasionally encountered in the large scale preparation of diphtheria toxin may be the result of failure to control completely the composition of the culture medium used, or of failure to use a unit of titration, such as the flocculation unit, which is independent of seasonal fluctuations in animal resistance.

AUTHORS' SUMMARY.

THE ETIOLOGY OF ERYSIPELAS, ESPECIALLY CHRONIC RELAPSING ERYSIPELAS. KARL BAERTHLEIN, Zentralbl. f. Bakteriol. **114**:271, 1929.

In eighteen cases of acute and chronic relapsing erysipelas, diphtheria bacilli and not streptococci were found. Autovaccines prepared from the diphtheria bacilli led to the cure of all but one patient, in whom death occurred too quickly for the vaccine to be used.

PAUL R. CANNON.

THE BEHAVIOR OF HERPES VIRUS IN TISSUE CULTURE. E. GILDEMEISTER, E. HAAGEN and L. SCHEELE, Zentralbl. f. Bakteriol. **114**:309, 1929.

The authors succeeded in carrying herpes virus (Basle III) through twenty-two passages in tissue culture, the virus having been absorbed by sterile rabbit testis and grown in a medium consisting of five parts of normal rabbit plasma and one part of spleen extract.

PAUL R. CANNON.

DEVELOPMENTAL STAGES OF THE SYPHILITIC VIRUS IN THE BLOOD. E. J. ROUKAVISCHNIKOFF, Zentralbl. f. Bakteriol. **115**:66, 1929.

The author kept the blood of syphilitic patients and of animals infected with syphilis for periods of several months and observed changes in it which he interprets as phases of a complicated life-cycle of *Spirochaeta pallida.* He considers the first stage of this cycle to consist of an avisual form, which later develops into a homogeneous substance. When stained red by Giemsa's method, it becomes transformed into coccoid forms, and these eventually become transformed into accumulations of spirochetes.

PAUL R. CANNON.

THE BACTERIAL FLORA OF THE SMALL INTESTINE IN PERNICIOUS ANEMIA. IDA LICHT, Zentralbl. f. Bakteriol. **115**:320, 1930.

The duodenal contents of eight patients with pernicious anemia, obtained through the duodenal tube, gave constantly positive cultures of *Bacillus coli,* whereas in normal persons the cultures were sterile. The observations were positive both in the stage of relapse and in the remission after liver therapy. The observations in patients with acidity, catarrhal icterus, cholecystitis and cholelithiasis are also given.

PAUL R. CANNON.

ON DISSOCIATION OF B. TYPHOSUS BY CULTIVATION IN TYPHOID-IMMUNE SERUM. G. M. FRAENKEL and M. W. STABNIKOWA, Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:539, 1930.

In studying two strains of *B. typhosus,* the authors found that under the influence of typhoid-immune serum, a succession of constant variants appear that differ in antigenic, biologic and cultural characteristics from the other strain.

Although these variants have as a basis many common characteristics, they show individual peculiarities in relation to the receptor apparatus and their ability to split carbohydrates. One can see the common characteristics between these variants and the paratyphoid group (agglutination by paratyphoid serums, the zone of acid agglutination and the splitting of dextrose by gas formation), but as a whole the corresponding characteristics of the variants are not absolutely those of *B. paratyphosus* and, in general, cannot be placed in any distinct species of the colon-typhoid group.

AUTHORS' SUMMARY.

Immunology

REACTIONS OF RABBITS TO NON-HEMOLYTIC STREPTOCOCCI. C. L. DERICK, C. H. HITCHCOCK and HOMER F. SWIFT, J. Exper. Med. **52**: 1, 1930.

The most satisfactory method thus far found for the induction and maintenance of a high degree of hypersensitiveness—"allergy," "hyperergy"—against nonhemolytic streptococci consists in the repeated production of small focal lesions with minimal doses of bacteria. After a preliminary sensitizing period of about two weeks' duration with either large initial, or small multiple daily inoculations, the later foci need be produced only at from seven to ten day intervals. Chronicity of low grade infection appears to be an important factor in the attainment of a high degree of hypersensitiveness.

AUTHORS' SUMMARY.

ENHANCED PASSIVE IMMUNITY TO STREPTOCOCCUS INFECTION IN RABBITS. F. P. GAY and A. R. CLARK, J. Exper. Med. **52**:95, 1930.

The experimental work herein reported tends to justify our hypothesis recently expressed, that the common failure of antibacterial serums to combat active infections when passively transferred to a normal animal is due not so much to a lack of suitable or sufficient antibodies as to absence of cell preparation or

mobilization in the recipient. In the case of experimental streptococcus empyema in the rabbit the course of the ordinarily fatal infection is in no wise affected by the transfer of the pleural fluid containing large numbers of mononuclear cells derived from an animal that is itself protected as a result of a nonspecific irritation. The serum of a rabbit highly immunized against the streptococcus and containing antibodies for it produces relatively slight effect in prevention or cure. In contrast to this the pleural exudate, either acute (polymorphonuclear) or subacute (mononuclear), produced in an actively immunized animal does protect passively to a considerable degree. In a similar fashion normal exudate cells of either type in combination with the relatively ineffective antiserum give a high degree of protection. It remains for further analysis to determine whether this form of passive immunity by antiserum enhanced by the addition of cells depends on the vital properties of the cells transferred or on their stimulation to cell mobilization in the recipient. And furthermore the extent to which this enhanced passive immunity may be effective in cure, and whether the cure is applicable to local or to both local and generalized infection remain to be seen.

AUTHORS' SUMMARY.

DEVELOPMENT OF AGGLUTININS AND PROTECTIVE ANTIBODIES IN RABBITS, AFTER INHALATION OF TYPE II PNEUMOCOCCI. ERNEST G. STILLMAN, J. Exper. Med. **52**:225, 1930.

Following repeated inhalations of the degenerated nonvirulent "R" forms of type II pneumococcus, no type-specific antibodies can be demonstrated in the serum of rabbits. Following repeated inhalations of slightly virulent type II (SAv) pneumococci, only protective antibodies can be demonstrated in the serum of rabbits. Following repeated inhalations of virulent type II (Sv) pneumococci, agglutinins and protective antibodies can be demonstrated in the serum of rabbits. Following repeated exposures of rabbits to inhalation of pneumococci, the type-specific response, evidenced by type-specific protective antibodies and agglutinins, varies in direct proportion to the virulence of the culture used.

AUTHOR'S SUMMARY.

A TYPE SPECIFIC SUBSTANCE DISTINCT FROM THE SPECIFIC CARBOHYDRATE IN PNEUMOCOCCUS TYPE I. JOHN F. ENDERS, J. Exper. Med. **52**:235, 1930.

Evidence has been presented for the existence of a substance distinct from the specific carbohydrate in the autolytic products of pneumococcus type I. The substance reacts specifically by precipitating homologous antiserum which either occurs naturally without antibody against the specific carbohydrate or has been deprived of that antibody artificially. In guinea-pigs passively sensitized with such antiserums the homologous autolysate containing the substance alone produces typical lethal anaphylactic shock. In weakly alkaline solution the substance is destroyed by boiling. In weakly acid solution it resists a temperature of 100 C. for at least one-half hour. Autoclaving for one hour at 15 pounds' pressure in either acid or alkaline solution destroys its activity as precipitinogen. The substance is resistant to peptic digestion. The chemical nature and the possible identification of the substance as a haptene have been discussed.

AUTHOR'S SUMMARY.

RESISTANCE OF NORMAL HUMAN BEINGS TO RECENTLY ISOLATED PATHOGENIC PNEUMOCOCCI. O. H. ROBERTSON and M. AGNES CORNWELL, J. Exper. Med. **52**:267, 1930.

With a view to obtaining information as to the virulence of pneumococci for human beings, a study was made of the pneumococcidal action of normal human serum-leukocyte mixtures for freshly isolated strains of pathogenic pneumococci. It was found that human beings as a group showed well marked pneumococcus-

destroying power in their blood for all types of organisms studied. Individuals, however, exhibited wide variations in their reactions against the different types. These ranged from marked killing effect for one type of pneumococcus to none or slight against another. While reactions against different strains within the type often varied considerably, this difference was less, on the whole, than that between types. An interpretation of these observations in the light of previous animal experiments in which actual determination of resistance to pneumococcus infection was made leads to the inference that human beings in general possess a considerable degree of natural immunity to all types of pneumococci but that individuals may be relatively susceptible to one or more types and at the same time resistant to others; also that pathogenic strains of pneumococci vary much in their virulence for man.

AUTHORS' SUMMARY.

OPSONIC AND BACTERIOTROPIN ACTION. MAX STRUMIA, STUART MUDD, E. B. H. MUDD, B. LUCKÉ and M. MCCUTCHEON, J. Exper. Med. **52**:299 and 313, 1930.

Antiserums against several strains of acid-fast bacteria have been separated into their euglobulin, pseudoglobulin and albumin fractions. The globulin fractions have been found to possess the essential properties of bacteriotropic serums; thus they alter the bacterial surface properties, and, in quantitative correspondence, cause agglutination and phagocytosis; these several effects withstand washing of the sensitized bacteria; the effects are little if at all affected by inactivation of the antiserums before fractionation; the combination of antibody and antigen is serologically specific. The conclusion is drawn that the contact of antigen with fresh homologous immune serum results in the deposit on the antigen surface of a substance or substances contained in the globulin fractions of the antiserum; as a consequence of this surface deposit leukocytes can spread on and engulf the antigen.

As a further test of the theory of tropin action proposed in the preceding paper, artificial surfaces have been prepared and have been found to be phagocytized according to prediction from the theory. Protein was adsorbed on collodion particles according to the technic of F. S. Jones. These particles were then agglutinated and prepared for phagocytosis by the corresponding protein precipitin serums. The precipitating, agglutinating, surface and tropin effects for each serum or serum globulin fraction have been found to be in satisfactory quantitative correspondence. All of these effects were serologically specific; all remained almost unaffected by inactivation of the immune serums for thirty minutes at 56 C. or by washing of the particles after sensitization. The surfaces of particles maximally sensitized by homologous rabbit immune serum or one of its globulin fractions have shown certain characteristic properties, i. e., they were cohesive, had wetting properties characteristic for protein and were isoelectric at p_H 5.5 to 5.8. The same set of properties was found for immune precipitate in the zone of maximal precipitation. The same properties have also been found for maximally sensitized acid-fast bacteria, and for maximally sensitized sheep erythrocytes. These results indicate, we believe, that precipitation, agglutination, the surface changes and increased phagocytosis are all consequences of one underlying phenomenon. This phenomenon is the specific chemical combination with, and deposit on the surface of the antigen of antibody protein. The several serologic reactions then follow as consequences of the properties of the sensitized surface and of the special environing conditions. The antibody is contained in the globulin fractions of immune serum, and appears to be a globulin with physicochemical differences from normal serum globulin.

AUTHORS' SUMMARIES.

EXPERIMENTS ON ANAPHYLAXIS TO AZOPROTEINS. K. LANDSTEINER and PHILIP LEVINE, J. Exper. Med. **52**:347, 1930.

Experiments with azoproteins containing stereochemical isomeric groups of d-tartaric acid and l-tartaric acid showed well marked specificity of the anaphy-

lactic reaction to these antigens, in conformity with the results of precipitin tests. Shock in these animals could be prevented by injection of azodye containing the specific groups. This phenomenon is ascribed to a desensitization.

AUTHORS' SUMMARY.

THE RELATION OF NATURAL HUMORAL ANTIPNEUMOCOCCAL IMMUNITY TO THE INCEPTION OF LOBAR PNEUMONIA. O. H. ROBERTSON, EDWARD E. TERRELL, JAMES B. GRAESER and M. AGNES CORNWELL, J. Exper. Med. **52**:421, 1930.

A study of the pneumococcidal-promoting action of the serum of patients with lobar pneumonia, secured from four to forty-eight hours after the onset of the disease, has revealed the fact that in the majority of instances the serum possessed the power to promote killing of the homologous pneumococcus, isolated in different instances from the lung, blood and sputum. While in some instances this action was slight, in others it was present to as great a degree as in normal persons and persisted as long as forty-eight hours or more after the beginning of the disease. The variations observed from case to case were not related to the extent of the pneumonic lesion or to the virulence of the several pneumococcus strains but appeared to depend on differences in individual human beings in respect to the natural antipneumococcus properties of their blood and their reaction to the invading micro-organism. A constant relationship was found to exist between the concentration of immune properties in the serum and blood invasion. In the presence of a well marked pneumococcidal-promoting power pneumococci were not found in the blood stream, and only when this property was greatly diminished or lost did blood invasion occur. The observations, which are supported by certain previous experimental observations, indicate that lobar pneumonia can occur in the presence of a normal circulating antipneumococcus defense mechanism. From this it is inferred that before pneumococcus growth can be initiated there must be present in the lung local changes of such nature as to provide conditions for the multiplication of pneumococci protected from the pneumococcidal action of the blood. Suppositions as to the nature of these changes and the establishment of the pneumonic lesion are discussed.

AUTHORS' SUMMARY.

IMMUNITY TO POLIOMYELITIS IN MOTHERS AND THE NEWBORN AS SHOWN BY THE NEUTRALIZATION TEST. W. LLOYD AYCOCK and S. D. KRAMER, J. Exper. Med. **52**:457, 1930.

Neutralization tests for the virus of poliomyelitis on blood serum of urban mothers and their new-born infants showed that immunity was present in ten of twelve (83 per cent) infants and in ten of twelve (83 per cent) mothers, with a complete correspondence between mother and infant. These tests point to passive transmission of immunity from mother to infant. Previous tests on other children (from 1 to 5 years of age) indicate that immunity in infants is transitory. Previous observations concerning the extent of immunity in urban adults are confirmed and extended. The results of these tests are in accord with the age distribution of poliomyelitis and parallel corresponding observations in diphtheria.

AUTHORS' SUMMARY.

SPECIFIC PRECIPITATION AND MOUSE PROTECTION IN TYPE I ANTIPNEUMOCOCCUS SERA. MICHAEL HEIDELBERGER, RICHARD H. P. SIA and FORREST E. KENDALL, J. Exper. Med. **52**:477, 1930.

A rapid and simple method is given for the approximate determination of the specifically precipitable protein in type I antipneumococcus serums. It is shown that a close parallel exists between the specifically precipitable protein and the number of mouse protection units in a wide variety of type I antipneumococcus serums. Owing to the consistent results obtained and the rapidity, simplicity and

economy of the method, its use is proposed instead of the mouse protection test as a basis for the titration of standard serums and the comparison of others with a standard. A method is given for conveniently preparing highly purified specific polysaccharide of type I pneumococcus.

AUTHORS' SUMMARY.

THE EFFECT OF INFLAMMATORY REACTIONS ON TISSUE IMMUNITY. FRANKLIN M. HANGER, J. Exper. Med. **52**:485, 1930.

Animals showing natural bacterial allergy to filtrates of *B. lepisepticum* survive infection by this organism more frequently than weak reactors. This increased resistance is manifested by better localization of infection. Bacterial filtrates injected into skin twenty-four hours before infection exert a nonspecific protection of that area against the organism, even in susceptible animals. The cells of this protected area seldom undergo necrosis when infected. Severe injury of tissues either by chemicals or by an antigen-antibody reaction produces a loss of local resistance even in immune animals. Mild injuries have the opposite effect. It is believed that in cases of severe injury, the affected areas undergo a segregation from the circulating antibodies. When bacterial-immune serum is injected with a protein antigen into the skin of a sensitized animal, a local alteration occurs in which substances necessary for the effective action of the immune serum are destroyed. A protective action is restored to the altered immune serum by addition of complement to the lesion. It is felt that allergy is not the chief mechanism in cellular resistance to infection; however, data are advanced which suggest that allergy does not exert local protection by acceleration of the immune processes and by rendering the cells locally refractory to further injury. Chronic infection by a single strain of organism excites cellular reactivity to many strains of bacteria often unrelated biologically. Hence a nonspecific mechanism for localizing infections throughout the body may be induced.

AUTHOR'S SUMMARY.

SEROLOGICAL REACTIONS IN PNEUMONIA WITH A NON-PROTEIN SOMATIC FRACTION OF PNEUMOCOCCUS. WILLIAM S. TILLETT and THOMAS FRANCIS, JR., J. Exper. Med. **52**:561, 1930.

Serums from persons acutely ill with lobar pneumonia possess the capacity to precipitate in high titer a nonprotein somatic fraction derived from pneumococci (fraction C). Following crisis the reaction is no longer demonstrable. Serums obtained from cases of pneumococcus pneumonia during illness and convalescence have been tested for antibodies specificially reactive with three chemically distinct constituents of pneumococcus. The results, when correlated with the course of disease, demonstrate differences in the occurrence of each qualitatively distinct antibody. The precipitation of pneumococcus fraction C is not limited to the serums of persons ill with pneumococcus infection. But in the few other cases available for comparative tests, definite reactions have been obtained only in streptococcus and staphylococcus infections and in acute rheumatic fever.

AUTHORS' SUMMARY.

CUTANEOUS REACTIONS IN PNEUMONIA. THOMAS FRANCIS, JR., and WILLIAM S. TILLETT, J. Exper. Med. **52**:573, 1930.

The majority of patients convalescent from pneumonia due to types I, II and III pneumococcus develop at the time of recovery circulating antibodies for the homologous type of organisms. At the same time an immediate wheal and erythema reaction followed the intradermal injection of the homologous type-specific polysaccharide in 100 per cent of type I patients, 58.8 per cent of type II patients and 44 per cent of type III patients. In a group of eighteen patients repeatedly tested with the type-specific polysaccharides, ten developed in the second or third week of convalescence circulating antibodies for one or more heterologous types.

In none of twenty-one control patients was this phenomenon observed. It is suggested that the development of circulating antibodies for heterologous types of pneumococcus was associated with the previous intradermal injections of the type-specific polysaccharides.

AUTHORS' SUMMARY.

IMMUNOLOGICAL STUDIES IN RELATION TO THE SUPRARENAL GLAND. J. MARMORSTON-GOTTESMAN, DAVID PERLA and JEFFERSON VORZIMER, J. Exper. Med. **52**:587, 1930.

Bilateral suprarenalectomy in rats lowers the resistance to a subsequent infection with *T. lewisi*. Almost 70 per cent of these rats die within an average period of 5.8 days after infection. The multiplication of the parasites in the circulating stream is not more considerable than in rats previously normal, nor is the duration of the disease in the surviving rats any longer than in the normal group. Bilateral suprarenalectomy does not prevent the formation of immune substances to the parasites but appears to lower the natural resistance of the rat to the toxic effects of the protozoan infection. The acquired immunity to *T. lewisi* of normal rats as a result of infection is not broken down by subsequent suprarenalectomy. Unilateral nephrectomy does not affect the course of a subsequent infection with *T. lewisi*.

AUTHORS' SUMMARY.

THE COMPLEMENT FIXATION TEST IN RELATION TO THE GONOCOCCUS AND ALLIED ORGANISMS. JOHN O. OLIVER, J. Hyg. **29**:259, 1929.

Under experimental conditions, in rabbits, a considerable degree of cross-fixation between *Micrococcus catarrhalis* antiserums and gonococcal extracts occurs in complement-fixation tests. The degree of cross-fixation under these experimental conditions is also well marked with aberrant forms of *M. catarrhalis* bearing a close resemblance to the more typical organisms, but is slight with those organisms showing considerable variation from the typical strains. Similar experiments carried out with patients are less successful in producing such cross-fixation, probably owing to the limitation of dosage and the method of administration imposed. Naturally occurring infections with *M. catarrhalis* and aberrant forms of the organism introduce a danger of cross-fixation in gonococcal complement-fixation tests. Such results appear, however, to be the exception rather than the rule in such infections. Serums giving strongly positive reactions to the Wassermann test do not tend to react to the gonococcal complement-fixation test in the absence of a history or of signs of the disease, and no danger of falsely positive reactions arises as a result of preparing gonococcal extracts from patients suffering from syphilis in the secondary stage in addition to gonorrhea.

AUTHOR'S SUMMARY.

THE TOXICITY OF HUMAN SERUM FOR THE GUINEA-PIG. SUSAN G. RAMSDELL and I. DAVIDSOHN, J. Immunol. **18**:473, 1930.

When normal horse serum was used in large amounts as an antigen in the human being, the phenomenon of a toxicity of the serum of such treated persons for the guinea-pig was found to occur more regularly and to continue for a longer period of time than had been shown to be the case in our former experiments with serums of persons treated with various immune serums. This increase is attributed to the relatively large amounts of serum with which the patients were treated. Certain cases were found in which the serum taken at a pretreatment bleeding contained the factor for toxicity. This was usually, but not always, accompanied with a higher than normal (heterophil) agglutinin titer for sheep red cells. Such serums tended to become more toxic subsequent to treatment of the patient along with an increase of the agglutinin and hemolysin titers. When the serums of a group of seriously ill patients were tested, the phenomenon of toxicity

was found with considerable frequency, especially in those suffering from syphilis and acute infectious processes. In 50 per cent of the serums of the last, the toxicity was correlated with the presence in the serum of heterophil antibody (sheep cell agglutinin in a titer above that normally found). It is evident that the toxicity of human serum for the guinea-pig must be ascribed to two or more different factors in the serum: one of these its content in heterophil antibody, the other as yet undetermined.

AUTHORS' SUMMARY.

QUANTITATIVE RELATIONS IN AGGLUTINATION AND PRECIPITATION. HANS ZINSSER, J. Immunol. **18**:483, 1930.

Zinsser would explain why agglutinating serum can be active in very much higher dilution than precipitating serum by assuming that in each case the antiserum must coat with its globulin the surfaces of the antigenic particles. Now the total surface of antigenic particles concerned in the precipitation test is estimated to be at least 10,000 times greater than the surface of the bacteria concerned in agglutination, and consequently a given serum might be diluted 10,000 times higher without losing its agglutinating power than could be done before it loses its power of precipitating colloidal antigenic particles. This explanation would eliminate objections to the unitarian conception of antibodies based on the fact that agglutinating serum can be diluted many more times without losing its agglutinating effect while its precipitating effect ceases on comparatively slight dilution.

BLOOD GROUP DISTRIBUTION AMONG POLYNESIANS. CLARA NIGG, J. Immunol. **19**:93, 1930.

The incidence of the four blood groups among 413 full-blooded Hawaiians was found to be as follows: group O, 36.5 per cent; group A, 60.8 per cent; group B, 2.2 per cent; group AB, 0.5 per cent. The A agglutinogen was found in 100 per cent of the 237 group A Hawaiian bloods examined for this factor. This incidence is in contrast to 80 per cent found in the white race.

AUTHOR'S SUMMARY.

USE OF BROTH CULTURE FILTRATES IN ANAPHYLAXIS EXPERIMENTS. JOHN Y. SUGG and JAMES M. NEILL, J. Immunol. **19**:145, 1930.

Experiments were made on two questions. First, the primarily toxic (anaphylactoid) action was studied by intravenous injection of normal guinea-pigs with formaldehyzed and unformaldehyzed filtrates of diphtheria and other bacilli and with the nonbacterial constituents of the filtrates (uninoculated broth, solutions of phenol and of formaldehyde). The possibility of sensitization to the nonbacterial constituents during immunization with the filtrates was studied by intravenous tests on animals previously given repeated subcutaneous injections of formaldehyde solution or of formaldehyzed broth. With diphtheria filtrates, neither the primary toxicity nor the possibility of sensitization to the broth constituents, introduced significant complications in their use as material for active sensitization and for subsequent intravenous tests. The adaptability of broth culture filtrates of other bacteria to anaphylaxis experiments would depend on the quantitative effectiveness of the antigens they liberate into their culture fluids.

AUTHORS' SUMMARY.

RENAISSANCE OF PRE-EHRLICH IMMUNOLOGY. W. H. MANWARING, J. Immunol. **19**:155, 1930.

There is convincing evidence that injected antigens undergo a series of chemical "hybridizations" in animal tissues, and suggestive evidence that the resulting antigen-tissue "hybrids" become semipermanently "symbiotic" with these tissues, both terms, of course, being used metaphorically. Whether or not these "symbiotic hybrids" are to be regarded as partially homologized antigens, as specifically

alienated somatic proteins or as antigen-somatic-protein conjugates cannot be predicted from present biochemical knowledge. There is convincing evidence that some of these antigen-tissue "hybrids" have properties simulating those of specific antibodies, but no proof thus far that they are identical with these antibodies. There is, however, no evidence at the present time that there is any other physiologic method of specific antibody formation.

AUTHOR'S SUMMARY.

ON THE NATURE OF THE THERMOPRECIPITINS. DINO D. NAI, J. Immunol. **19**: 255, 1930.

The agglutinogen of Joos, the thermostable precipitinogen of Ascoli, the residue antigens of Zinsser and the carbohydrate material of the American observers may be representatives of a single class of antigens. Their serologic reactions are parallel and their common characteristic is heat stability. On these grounds it is possible that the carbohydrate nature of the soluble specific substance of the American observers may also exist in the antigens of Ascoli, Joos and Zinsser. Indeed, this idea is supported by the recent experiments of Schockaert. He found that the thermostable antigen involved in the Ascoli reaction with anthrax bacilli, whether pure cultures of the micro-organism or organs of anthrax-infected animals are employed, is a polysaccharide similar to that of the soluble specific substance of pneumococci, or of other bacteria.

AUTHOR'S SUMMARY.

ANTIGENS FROM CULTURES OF TREPONEMA PALLIDUM. AUGUSTUS B. WADSWORTH, JEANNE E. VAN AMSTEL and MARGARET W. BRIGHAM, J. Immunol. **19**:289, 1930.

One strain of *Spirochaeta pallidum* was used for this study. By the aqueous extraction of the organisms, antigenic substances were obtained which reacted with serums of rabbits immunized with the homologous strain, but not with syphilitic rabbit or human serums. Cholesterol added to various extracts of the organisms did not increase their sensitivity, and alcoholic extracts were anticomplementary. The antigenic substances obtained by aqueous extraction of the organisms appear to differ from those obtained by alcoholic extraction. Substances that reacted with rabbit immune serum and rabbit and human syphilitic serums were found in alcoholic extracts of the culture medium, and similar extracts of mediums containing the spirochete were more active. Cultures of spirochetes produced complement-fixing substances like those obtained by aqueous extracts of spirochetes free from medium.

E. DELVES.

COMPLEMENT AND OPSONIN. J. GORDON, J. Immunol. **19**:303, 1930.

Congo red and similar dyes prevent the bactericidal and hemolytic (complement) activities of normal serum. A serum the complement of which has been inactivated by certain concentrations of congo red is still able to exert its opsonic activity.

AUTHOR'S SUMMARY.

ON THE PRODUCTION OF TYPHOID AGGLUTININS. C. A. BEHRENS and C. H. KEIPPER, J. Immunol. **19**:321, 1930.

Frequency of injections plays a major rôle in typhoid agglutinin production. A close relationship exists between the interval of injections and the dose employed. Total amounts of agglutinogen injected have but little direct influence, however, some indirect influences are apparent. The axiom of frequent stimulation of the body cells of the animal by the use of small doses of agglutinogen and by larger doses as the intervals between inoculations are increased is emphasized. Typhoid agglutinins with greatest potencies are produced by injecting 0.1 cc. frequently, 1 cc. less frequently and 5 cc. still less often. Typhoid agglutinins with high titers are possible with any of the three doses studied; the highest, however, follow the

employment of the largest dose. Typhoid agglutinins of equal potencies are elaborated irrespective of dosage, when inoculations are made every third day. Increasing the dose with each subsequent injection results in agglutinins with much higher titers than when the reverse is true. Nonspecific agglutinin formation is negligible. Physical deterioration of the rabbits shows its effect on agglutinin production. Comparable results are obtained with various agglutinogens, precipitinogens and lysinogens.

AUTHORS' SUMMARY.

IS IMMUNITY TO SCARLET FEVER A FACTOR IN PUERPERAL SEPSIS? LELAND W. PARR, J. Prev. Med. **4**:105, 1930.

A very favorable puerperal morbidity rate (9.33 per cent) was observed in a study of more than 1,000 deliveries in the hospital of the American University of Beirut, Syria, a region of high scarlet fever immunity. The question is raised as to the possibility of this favorable rate being due to a group immunity within the streptococcus group.

AUTHOR'S SUMMARY.

THE RESISTANCE TO POLIOMYELITIS OF ANIMALS PREVIOUSLY INOCULATED WITH HEATED VIRUS. HOWARD J. SHAUGHNESSY, PAUL H. HARMON and FRANCIS B. GORDON, J. Prev. Med. **4**:157, 1930.

Monkeys that had received single intracerebral inoculations of poliomyelitis virus heated at from 42.5 to 55 C. for from five to sixty minutes failed in most instances to show an appreciable degree of immunity to subsequent inoculation with active virus. There are, however, indications that those monkeys that had received the virus heated at 45 or 50 C. were relatively immune. Attempts to immunize monkeys with repeated inoculations of virus did not prevent paralysis, but on the contrary seemed to heighten predisposition. Apparently, however, the case-fatality rate was lowered.

AUTHORS' SUMMARY.

IMMUNITY TO INFANTILE PARALYSIS. W. LLOYD AYCOCK and S. D. KRAMER, J. Prev. Med. **4**:189, 201, 1930.

Additional observations are recorded concerning immunity to poliomyelitis as indicated by the neutralization of the virus by the blood serum of: persons who had had an attack of the disease, monkeys that had passed through the experimental disease, monkeys immunized with the virus, normal monkeys and normal persons of different ages from urban and rural populations. These tests in normal individuals are in conformity with extended previous observations that a widespread immunity to poliomyelitis exists among individuals not known to have had the disease. Additional evidence is afforded that this immunity originates in exposure to the virus and, from the extent to which it occurs and the order in which it develops, that the virus spreads by contact of person with person.

Serums of twenty-one adults from Atlanta, Georgia, having no history of poliomyelitis, unquestionably neutralized poliomyelitis virus in eighteen instances, and failed to neutralize it in two instances; the results with the other serum were not clearcut, but apparently this serum should be counted as having neutralizing power. These tests indicate that immunity to poliomyelitis is equally extensive in warmer and cooler climates, and therefore suggest that the extent of the distribution of the virus in warmer climates is equal to that in cooler climates.

AUTHORS' SUMMARY.

THE RELATIVE INSUSCEPTIBILITY OF YOUNG RABBITS TO STREPTOCOCCAL TOXIN. H. J. PARISH and C. C. OKELL, J. Path. & Bact. **33**:527, 1930.

When small rabbits (from 0.33 to 1 Kg.) and large rabbits (2 Kg.) are given intravenous injections with suitable doses of broth cultures of scarlet fever strepto-

cocci or scarlet fever toxin, the small rabbits survive for significantly longer periods. The relative insusceptibility of small rabbits to streptococcal toxin is paralleled to some extent by the observations of Cooke and others on the Dick test in young children. The susceptibility of small rabbits could not be increased by artificial sensitization.

AUTHORS' SUMMARY.

PHAGOCYTOSIS BY BRONCHIAL EPITHELIUM IN THE LUNGS OF MICE. E. S. DUTHIE, J. Path. & Bact. **33**:547, 1930.

Phagocytosis of red blood cells in the bronchi of the lung has been described in a case of extreme passive congestion in a mouse following irradiation. The phagocytic cells have been identified by their morphologic and tinctorial appearance, as well as by the compensatory hyperplasia in the surrounding epithelium, as being of epithelial origin. Bronchial dust cells have been studied in healthy mice and a multiplication in their number followed on the inhalation of carbon particles. From the evidence it is considered that these are also of epithelial origin.

AUTHOR'S SUMMARY.

EXPERIMENTAL STREPTOCOCCAL INFECTION AND IMMUNITY. A. W. DOWNIE, J. Path. & Bact. **33**:563, 1930.

Lesions in rabbits injected with living cultures of Dick and Dochez strains of scarlatinal streptococci were similar to those produced by toxin of the Dochez strain except for the localization of organisms in joints and muscles, and anemia and hemolysis in animals injected with living culture. The course of infection following intravenous injection of streptococci is described, and the effect of age and the virulence of the injected culture noted. Intradermal injection of the moderately virulent Dochez strain in fatal cases caused only a slight local reaction, and invasion of the blood stream was rare. In a highly virulent erysipelas strain the lesions were more extensive, and the blood stream was invaded some time before death.

Rabbits immunized with Dochez strain toxin were protected against death from the injection of the culture of this strain. The Dick scarlatinal strain acted similarly, and there was no evidence of protection against heterologous strains. Immunization with heat-killed cultures yielded no protection. No antitoxin or protection for mice was found in the serums of animals immunized with toxin or heat-killed cultures. The immunization with a toxin of a virulent strain gives no protection for the homologous or heterologous strains, but gives some protection against less virulent strains.

Filtrates of strains of high and low virulence show no difference as judged by skin tests. Rabbits repeatedly injected with killed cocci of the virulent erysipelas strain gave protection against the homologous strain but not against the moderately virulent Dochez strain. The serums of these animals protected mice against homologous, but not heterologous, strains.

It would seem that with the highly toxigenic, moderately virulent scarlatinal strains used, the action is antitoxic rather than antibacterial; with highly virulent strains, however, effective immunity would appear to be antibacterial rather than antitoxic, and type specific.

FROM AUTHORS' SUMMARY.

BACTERIOPHAGE ACTIVITY AND THE ANTIGENIC STRUCTURE OF BACTERIA. F. M. BURNET, J. Path. & Bact. **33**:647, 1930.

Lysis by bacteriophage requires a preliminary adsorption of the phage particles to the bacterial surface. Evidence has been given to show that the adsorption is highly specific and that the nature of the bacterial surface in respect of this adsorptive power is the chief factor determining whether the organism will be lysed by a given phage. The bacterial surface constituents responsible for the specific

adsorption of phage are not destroyed by heating to 100 C. and show a striking but incomplete parallelism in their functional aspects with the heat-stable agglutinogens. Organisms with similar heat-stable antigens despite wide differences in other respects show similar reactions toward bacteriophage and when the normal heat-stable antigen is replaced by another in the S-R transformation, a striking change in behavior toward phage occurs. On this evidence the hypothesis was put forward that bacteriophages and stabilotropic agglutinins were both specifically adsorbed to the same surface elements of bacteria. Further work showed that this hypothesis was inadequate to account for two groups of facts that some phage-resistant variants may show no serologic change and that serologically identical rough strains often show differences in phage reactions which can be related to the differing phage reactions of their smooth strains of origin. From a detailed study of the phage reactions and antigenic structure of various derivatives of three bacterial species, *B. sanguinarium* as a typical *Salmonella,* the Flexner type of dysentery bacilli and a white staphylococcus, an attempt is made to represent diagrammatically the constitution of the surface elements involved in the two types of function. The connection between the two functions is so intimate that one is justified in assuming that a single unit is responsible for both. In the *Salmonella* group this unit must be of considerable complexity to allow for the "unmasking" effect which is characteristic both of serologic and of phage reactions, when the S-R change takes place. The conditions in the particular staphylococcus studied seem to represent a simpler form of mosaic antigenic structure.

AUTHOR'S SUMMARY.

OBSERVATIONS ON THE VARIANTS OF B. SUBTILIS AND THEIR RELATION TO THE SOMATIC AND FLAGELLAR ANTIGENS. N. C. GRAHAM, J. Path. & Bact. **33**:665, 1930.

Four variants of *B. subtilis* (two motile and two, as a rule, nonmotile) have been obtained by selecting colonies on agar of different appearance. I and III form smooth, round, shiny colonies with regular margins; II forms "medusa-head" colonies and IV slightly irregular colonies with uneven surface and a somewhat granular texture. None of these variants has the distinctive characters of the R variants of *B. typhosus, paratyphosus,* etc. All four variants have the same heat-stable (100 C.) somatic antigen for which corresponding somatic agglutinins can be obtained. Only one somatic antigen has been demonstrated in the four variants of the three strains which have been examined in detail. Variants I and II are motile and contain, in addition, a heat-labile (100 C.) H or flagellar antigen and agglutinate with appropriate H agglutinins in a characteristic flocculent manner. The H antigen is the same for both motile variants. Variants with "medusa-head" colonies occur independently of any serologic or antigenic change. The nonmotile variants III and IV are coherent and viscous. They correspond when completely nonmotile to the O variant of Weil and Felix. The I and III variants consist of short bacilli. In IV the bacilli are perhaps somewhat longer than in I and III. Variant II, which forms "medusa-head" colonies, consists chiefly of very long rods, threads and chains. Of seven strains examined, only three agglutinated with the serums made from one of them; the remaining four did not appear to have any common antigen with those used to make serums.

AUTHOR'S SUMMARY

THE ACTION OF CERTAIN DYES ON THE BACTERICIDAL ACTIVITY OF NORMAL SERUM AND ON HAEMOLYTIC COMPLEMENT. J. GORDON, J. Path. & Bact. **33**:689, 1930.

The action of congo red in interfering with complement activity is not due to its adsorption to the red cell. The inhibitory effect of congo red on complement can be removed by adding adsorbing agents, e. g., charcoal, heated serum, serum albumin or serum globulin. The congo red is adsorbed on the complement and most probably on the serum protein.

AUTHOR'S SUMMARY.

TRANSMISSION OF MATERNAL IMMUNITY. J. H. MASON, T. DALLING and W. S. GORDON, J. Path. & Bact. **33**:783, 1930.

In sheep, beef, dog and horse no evidence of placental transmission of antitoxin was obtained.

THE VIRULENCE TYPES OF STREPTOCOCCI AND THEIR IMMUNOLOGIC RELATIONSHIPS. H. DOLD and H. R. MÜLLER, Zentralbl. f. Bakteriol. **114**:275, 1929.

The authors retested by intracutaneous injections into rabbits the virulence of strains of streptococci which had previously been classified in three grades of virulence on the basis of similar tests several months before. They noted a marked tendency for the organisms to maintain their type virulence. Furthermore, immunization against a lethal dose of the most virulent type was possible not only with the same strain but also with strains from the two less virulent types, thus indicating the lack of any marked difference in antigenic properties of strains of various degrees of virulence.

PAUL R. CANNON.

RELATIONSHIP BETWEEN HERPES AND VACCINIA IMMUNITY. E. GILDEMEISTER and PAUL HILGERS, Zentralbl. f. Bakteriol. **114**:314, 1929.

Further experiments tend to confirm the earlier ones of Gildemeister and Herzberg concerning the immunologic relationships between herpes and vaccinia. In a considerable percentage of experimental animals, vaccinia immunity exerts a protective effect against a herpes infection and herpes immunity exerts a similar effect against vaccinia infection. This protective effect is not especially high, but nevertheless is definitely present.

PAUL R. CANNON.

T-ERYTHROCYTES AND T-AGGLUTININS. C. HALLAUER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:15, 1930.

In 1927, Thomsen showed that under certain circumstances human red cells undergo such changes that they are agglutinated by human serum of all groups. Subsequently it was found that this change may be caused in various red cells by certain bacteria and their culture filtrates. The red cells are said to acquire a new receptor, "T," corresponding to which "T-agglutinins" exist in human and certain other normal serums. Hallauer has succeeded in immunizing rabbits and guinea-pigs with T-erythrocytes. The newly produced T-agglutinins are specific so far as they are absorbed only by T-erythrocytes.

A COMMON ANTIGEN IN HUMAN RED CELLS AND IN SHIGA'S BACILLUS. M. EISLER, Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:38, 1930.

The serum of a goat immunized with Shiga bacilli agglutinated human red cells of all groups and various strains of Shiga bacilli absorbed from immune goat serum the agglutinin for the bacilli as well as the agglutinin for red cells. The red cells, however, removed only the hemagglutinin.

THE INFLUENCE OF ANTIRABIC INOCULATIONS ON EXPERIMENTAL TUBERCULOSIS IN GUINEA-PIGS. M. P. GLUSMAN and J. I. GOLDENBERG, Ztschr. f. Immunitätsforsch. u. exper. Therap. **67**:187, 1930.

Antirabic inoculations do not accelerate the course of tuberculosis, and immunity to rabies develops as usual in tuberculous guinea-pigs.

THE ANTIGENIC PROPERTIES OF BACTERIOPHAGE. T. YOSHIZUMI, K. NAGASE and S. HOSOYA, Japanese J. Exper. Med. **8**:215, 1930.

Using a new method of purification, the bacteriophage yielded none of the color reactions for proteins and it contained only an extremely small amount of

nitrogen. The purified phage had as high a lytic power as the nonpurified. No difference could be found in the antigenic qualities of the purified and the unpurified phage. The purified phage does not act as a anaphylactogen or precipitinogen in its immune serum. The hypothesis that phage is a chemical, nonprotein substance is upheld.

Tumors

PRIMARY SYMPATHICOBLASTOMA OF THE SKIN OF THE THIGH. VICTOR C. JACOBSEN and KIYOSHI HOSOI, Am. J. Path. **6**:427, 1930.

A case of sympathicoblastoma, primary in the skin or subcutaneum of the thigh of an infant, aged 9 months, is here reported. There was a recurrence in the same location within six months. So far as we have been able to determine, this is the only instance of a sympathicoblastoma occurring in such an unusual location. At the present writing, almost two years after the removal of the recurrent tumor, the child is vigorous, robust and apparently normal in every respect.

AUTHORS' SUMMARY.

THE SIGNIFICANCE OF THE MUSCULAR "STROMA" OF ARGENTAFFIN TUMORS (CARCINOIDS). P. MASSON, Am. J. Path. **6**:499, 1930.

Originating in the nerves of the mucosa, previously hypertrophied, carcinoids penetrate the myenteric plexuses progressively without destroying them and without provoking their hyperplasia. They merit the name of neurocarcinoid. Invasion of the connective tissue and of the lymphatics is secondary. Connective tissue infiltrated by carcinoids does not originate muscle fibers. On the contrary, when the nerves are invaded by carcinoids, the corresponding muscle coats undergo hyperplasia restricted to the territory of the infected nerve. The muscle fibers formed in the interstices of carcinoids, then, are not an integral part of these tumors; they result from proliferation of preexisting muscles provoked by the presence of argentaffin cells in their nerves. This myogenic action of the argentaffin cells seems due to a product of limited diffusibility secreted by the cells into the nerves (neurocrinia). As a working hypothesis, one may suppose that the normal argentaffin cells of the intestinal mucosa function like the cells of carcinoids, and that their secretion poured into the plexus of the mucosa plays a rôle in the functioning of the muscularis mucosae.

AUTHOR'S SUMMARY.

DIAGNOSIS OF INTRACRANIAL TUMORS BY SUPRAVITAL TECHNIQUE. LOUISE EISENHARDT and HARVEY CUSHING, Am. J. Path. **6**:541, 1930.

The supravital technic has been adopted as the most favored routine method of diagnosing and classifying tumors of the central nervous system, it being of particular value in the cytologic differentiation of the various types of gliomas. Not only can an immediate diagnosis be given to the surgeon so that he may learn to associate the microscopic type of the lesion with its gross appearance at the operating table, but a permanent photographic record of the fresh preparations can be made for comparison with the permanent section of the fixed tissue. The supravital method makes it possible for the examiner to see the cells with their cytoplasm and processes intact and gives pictures which are wholly unfamiliar to those who have only studied these cells in fixed sections.

AUTHORS' SUMMARY.

SKELETAL METASTASES IN CARCINOMA OF THE THYROID. ISAAC LEVIN, Am. J. Path. **6**:563, 1930.

Three cases of metastases in the skeleton secondary to carcinoma of the thyroid are reported. In all three cases the clinical symptom complex as well as the

evident pathology was caused by tumors in the bone. While the primary tumor in the thyroid was insignificant, pathologically as well as clinically, compared with the condition in the skeleton, as a result in all three cases, the primary condition was overlooked. Whenever a diagnosis of malignant tumor in the skeleton, single or multiple, is made, a search must be undertaken for a primary malignant tumor elsewhere before the diagnosis of a primary malignant tumor in the skeleton can be made. In such a search for a primary malignant tumor, in a female, next to the breast, the thyroid must be thought of, and in a male, next to the prostate, the thyroid must be considered as the most probable seat of a primary tumor. Such a diagnostic analysis is of importance not only from the theoretical but also from the practical clinical standpoint.

AUTHOR'S SUMMARY.

BIOPSY BY NEEDLE PUNCTURE AND ASPIRATION. H. E. MARTIN and E. B. ELLIS, Ann. Surg. **92**:169, 1930.

Aspiration of tumor masses through an 18 gage needle by a syringe avoids dissemination of tissue, hemorrhage, infection and scars in visible areas. This method has led to a correct diagnosis in 60 per cent of sixty-five cases examined. These included tissues obtained from the neck, antrum, lungs, breast and bones. The method of preparing the specimen for immediate and paraffin section is also given.

RICHARD A. LIFVENDAHL.

MALIGNANT TUMORS AND THEIR METASTASES. J. E. MCWHORTER and A. W. CLOND, Ann. Surg. **92**:434, 1930.

This article represents a summary of 865 autopsies at Bellevue Hospital of New York, on malignant tumors, which comprised 6 per cent of 13,500 necropsies, covering a period of twenty-three years. The location of the primary tumor and the occurrence of regional and distal metastases are tabulated and discussed.

RICHARD A. LIFVENDAHL.

FAILURE OF SPLEEN FROM TUMOR-BEARING ANIMALS TO PRODUCE TUMORS. W. H. WOGLOM, J. Cancer Research **13**:305, 1929.

Experiments were reported by some German observers, in which the injection of an emulsified spleen from tumor-bearing rats into normal rats was sometimes followed by the appearance of a tumor in the healthy rodents. The experiments, if confirmed, are of interest in that they would destroy the established conception that cancer can be transmitted only by virtue of its cellular elements.

In a series of experiments, which he describes in detail, Woglom could not corroborate the observations of the continental worker. He is wondering whether the splenic tissue from the tumor-bearing rats used in Germany did not contain metastases at the time of transplantation.

B. M. FRIED.

SPONTANEOUS MAMMARY CANCER IN MICE. MILLARD C. MARSH, J. Cancer Research **13**:313, 1929.

Marsh studied two lines or strains of albino mice which spontaneously develop cancer of the breast. One strain yields the tumor in about 90 per cent and the other in about 55 per cent of the breeding females. These strains showed by mere inspection convincing evidence of heredity in various characters, including the disease cancer. Crosses of these strains with wild mice showed for cancer inconclusive evidence of simple mendelian inheritance with dominance.

In general, Marsh is of the opinion that the origin of tumors in mice is controlled by heredity and is affected as well by many environmental factors, some of which are little known or commensurable. This tends to obscure the genetic

interpretation. It is probable that the expression of the tumor in heterozygotes is variable, and mendelian dominance or recessiveness is not sharply defined.

B. M. FRIED.

THE ACTION OF CERTAIN DYESTUFFS ON THE GROWTH OF TRANSPLANTABLE TUMORS. K. SUGIURA and S. R. BENEDICT, J. Cancer Research **13**:340, 1929.

Following the early experiments of Wassermann and his associates to the effect that by injecting a solution of selenium-eosin into the blood stream of cancerous mice the eosin would carry colloidal selenium into the tumors, numerous workers attempted to treat cancer-bearing animals with dyes. The results obtained were contradictory, or negative. Sugiura and Benedict studied the influence of a preliminary treatment in vitro of certain dyestuffs on the subsequent growth of malignant neoplasms in rats and chickens. For their elaborate experiments they found that malachite green possessed the greatest destructive action on the tumors studied and congo red the least, while methylene blue (methylthionine chloride, U. S. P.) and gentian violet were intermediate in action. The harmful action of the dyestuffs is at least partially due to the selective staining reactions, i. e., the adsorption of dye by proteins of tumor elements, and to the effect of the hydrogen ion concentration of the dye solutions.

B. M. FRIED.

ON THE FAILURE IN HETEROPLASTIC TRANSPLANTATION OF HUMAN MAMMARY CARCINOMAS INTO THE BRAINS OF RATS. JOHN J. MORTON, J. Cancer Research **13**:359, 1929.

Morton attempted to transplant human mammary cancer into the brains of albino rats. Two hundred rats and twenty different human breasts with actively growing cancer were used in the experiments. In no instance did a tumor develop in the brains of the rodents. The inoculated neoplastic tissue was found to be transformed into hyalinized connective tissue.

B. M. FRIED.

THE CARCINOGENIC ACTIVITY OF TAR IN VARIOUS DILUTIONS. W. H. WOGLOM and L. HERLY, J. Cancer Research **13**:367, 1929.

The authors attempted to induce cancer in mice by painting their backs with various dilutions of tar in glycerin. They found that a dilution down to 25 per cent neither retards the appearance of malignant tumors nor diminishes the number induced. However, the mortality of the experimental animal is about 50 per cent lower when the diluted tar is used.

B. M. FRIED.

SPONTANEOUS TUMORS OF THE RAT. F. D. BULLOCK and M. R. CURTIS, J. Cancer Research **14**:1, 1930.

Within a period of ten years, in a colony of about 10,000 rats, the authors have found 2,450 rats each bearing 1 or more cysticercus tumors and 489 rats with tumors which arose independently of the direct stimulation of the parasite. Sarcoma was by far the most common form of malignant new growth. There were 63 carcinomas, 35 of which were of the squamous cell type, involving the skin in 24 rats, the uterus in 10 and the lung in 1. There also were mixed tumors and rare tumors, such as chondrorhabdomyosarcoma and ostochondrosarcoma.

The superficial tumors rarely metastasized, but the more deeply seated tumors not infrequently formed metastases.

Of 212 benign tumors, 87 originated in the mammary gland in contrast to the low incidence of cancer of the breast. Seventy-four tumors arose in the thymus and of these 68 were benign.

An interesting trait of the rat neoplasms was the comparatively frequent occurrence of a malignant transformation of the fibrous tissue elements in the benign

fibrous and fibro-epithelial tumors and also in the malignant epithelial tumors. The occurrence of primary multiple tumors was also not as rare as one finds in the literature. There were very few primary pulmonary tumors.

B. M. FRIED.

URANIUM-THORIUM COLLOID IN THE TREATMENT OF CARCINOMA. G. T. PACK and F. W. STEWART, J. Cancer Research **14**:152, 1930.

The authors treated eight patients with intravenous injections of uranium-thorium after the manner recommended by Hockins. There was no evidence of improvement following the treatment. In two patients the chemical was found deposited in the Kupffer cells and in the reticulo-endothelial cells of the spleen. In these cases the desiccated livers and spleens were radioactive, whereas the desiccated tumor tissues showed no evidence of radioactivity. B. M. FRIED.

THE AGE AND SEX DISTRIBUTION AND INCIDENCE OF NEOPLASTIC DISEASE AT THE MEMORIAL HOSPITAL, NEW YORK CITY. G. T. PACK and R. G. LEFEVRE, J. Cancer Research **14**:167, 1930.

Of 19,129 tumors studied at the Memorial Hospital, New York, within a period of twelve years, 16,565 were malignant. Of these 89.6 per cent were epithelial and 10.4 per cent of connective tissue origin (sarcomas). The average age of patients with carcinoma was 53.9 years, and of those with sarcoma, 38.2 years. Tumors of the brain were uncommon in old people. Fifty per cent of the gliomas were in subjects younger than 25 years. The average age of persons with Ewing's tumor was 22 years. Multiple myeloma occurred in patients of about 42 years. Cancer of the alimentary tract was four times as frequent in men as in women. Cancers of early life, as in the breast, stomach, tongue and rectum, progress more rapidly, disseminate more frequently and recur more often after removal than do their congeners of adult life. Radiosensitivity is a property found frequently in the malignant neoplasms of youth.

This article, which occupies practically the entire number of the *Journal of Cancer Research*, abounds in tables and figures. It is only partially abstracted.

B. M. FRIED.

THE BLOOD CHEMISTRY OF HENS BEARING ROUS SARCOMA, NO. 1. J. H. ROE and HELEN M. DYER, J. Cancer Research **14**:301, 1930.

Twelve hens bearing Rous sarcoma no. 1 showed no change in the nonprotein nitrogen, uric acid, creatinine, chlorides, cholesterol, serum calcium and inorganic phosphorous, hemoglobin and bilirubin of the blood. The analyses were performed at times varying from eighteen days before death to the day of death. The blood sugar of the sarcomatous hens was found to be elevated. There was a questionable lowering of the carbon dioxide combining power of the blood of the tumor-bearing birds.

B. M. FRIED.

A CRITICAL STUDY OF VITAMIN A AND CARCINOGENESIS. K. SUGIURA and S. R. BENEDICT, J. Cancer Research **14**:306, 1930.

For about eighteen months the authors followed up 108 rats fed a diet deficient in vitamin A, to ascertain whether such alimentary regimen would play a rôle in the development of tumors in these rodents. The results obtained are to the effect that the prolonged maintenance on a deficient diet has no apparent influence on tumor genesis in these animals.

B. M. FRIED.

THE INFLUENCE OF HIGH DIETS ON THE GROWTH OF CARCINOMA AND SARCOMA IN RATS. K. SUGIURA and S. R. BENEDICT, J. Cancer Research **14**:311, 1930.

The percentage of positive tumor inoculations and the growth rate of Flexner-Jobling rat carcinoma in rats were diminished, and the number of tumor regres-

sions were increased, by feeding the animals with an excessive amount of butter fat (over 2.6 Gm. daily).

Ingestion of a high fat diet failed to show any inhibiting or accelerating influence on the growth of Sugiura rat sarcoma.

The number of takes and the growth rate of rat carcinoma and rat sarcoma were not affected by feeding animals with a fat-free diet.

The vitamins A, C, D and E are not essential for the growth of transplanted neoplasms.

AUTHORS' SUMMARY.

THE CATALYTIC EFFECT OF METHYLENE BLUE ON THE OXYGEN CONSUMPTION OF TUMORS AND NORMAL TISSUES. E. S. GUZMAN BARRON, J. Exper. Med. **52**:447, 1930.

Methylene blue (methylthionine chloride, U. S. P.) has no catalytic effect on the oxygen consumption of the normal adult tissues that do not possess aerobic glycolysis. The dye increases the oxygen consumption of these tissues when their respiration has been inhibited by the addition of potassium cyanide and their fermentative power has thus been brought into action. Methylene blue increases the oxygen consumption of normal tissues having aerobic glycolysis, and of tumors. The effect of methylene blue is roughly proportional to the fermentative power of tissues.

AUTHOR'S SUMMARY.

STUDIES OF DISEASES OF THE LYMPHOID AND MYELOID TISSUES. HENRY JACKSON, JR., FREDERIC PARKER, JR., and EUGENE C. GLOVER, J. Exper. Med. **52**:547, 1930.

From a study of the metabolism of seventy-one lymph nodes and tumors one may conclude: The nature of a tumor cannot be predicted from the metabolism because too much overlapping of metabolic rates exists between the pathologic groups. There is no evidence metabolically one way or another as to whether malignant lymphomas of any type should be classed as neoplastic or as infectious processes. The degree of cell differentiation can in most cases be foretold by the percentage difference between the aerobic and the anaerobic glycolysis. The greater the differentiation the greater is the percentage difference. Sarcomas in general constitute an exception to this rule. The degree of malignancy in carcinoma, but not in other tumors, can, with certain exceptions, be predicted from the height of the value U. Human sarcomas appear to have a metabolism far more closely comparable to that of benign tumors than to that of carcinomas. They do not behave as malignant tumors under the Warburg classification. Their energy requirements are not of the same order as those of carcinoma. One cannot from the value U or from the glycolytic rates predict whether or not a tissue should be classed as neoplastic. Warburg's observations on carcinomas are confirmed and amplified.

AUTHORS' SUMMARY.

CARCINOGENIC SUBSTANCES AND THEIR FLUORESCENT SPECTRA. E. L. KENNAWAY and I. HIEGER, Brit. M. J. **1**:1044, 1930.

Heat was found to be a factor in producing carcinogenic substances in acetylene, isoprene, cholesterol, human skin, muscle and hair, and in yeast. These substances caused cancer in mice. While working with substances of a carcinogenic nature at body temperatures, the authors found these producing typical spectra in the 4,000 to 4,400 Angström unit bands. At times there was some confusion in the bands because certain impure hydrocarbons apparently contained several fluorescent compounds. Some fluorescent substances did not produce cancer, and several explanations are offered to account for the fact. There may be this spectrum produced by carcinogenic and also noncarcinogenic substances. Also the fluorescent test is very delicate, often appearing in dilutions of 1 : 200,000,000, in which strength

it could not reasonably be expected to produce cancers in mice. It is suggested that a spectroscopic test be applied to materials suspected of carcinogenic effects such as lubricating oil.

GEORGE RUKSTINAT.

EPIDERMOID CARCINOMA OF THE HEAD AND NECK. RUPERT A. WILLIS, J. Path. & Bact. **33**:501, 1930.

Epidermoid carcinoma of the head and neck frequently invades the internal jugular or other main cervical veins, producing an intravascular thrombus permeated by malignant cells, a condition present in twelve of the twenty unselected cases of the present series. Remote visceral metastases from craniocervical epidermoid cancer are by no means infrequent, and were present in ten of the twenty cases described, or (including a subsequent series) in seventeen of thirty-five cases. The origin of visceral deposits in these cases is invariably to be found in malignant penetration of the lumen of the main veins in the neck. Macroscopic pulmonary metastases frequently but not invariably develop following the liberation of malignant emboli from the cervical veins. The explanation of the absence of visible metastases in the lungs in cases presenting visceral deposits elsewhere is discussed. The liver is the most frequent site of development of systemic metastases, and as evidenced by the number of mitoses present hepatic tissue is a highly fertile soil for epidermoid cancer cell multiplication. Established visceral metastases frequently penetrate adjacent veins in a manner similar to that described in the neck, thus establishing new malignant embolic cycles. Penetration by a hepatic metastasis of branches of the portal vein in the liver results in further dissemination of malignant cells to other parts of the viscus, which in this way may become heavily sown with secondary growths. Penetration of a tributary of the portal vein by a metastasis in one of the organs in the area of portal drainage, e. g., the spleen, may also produce a further brood of hepatic deposits. Hepatic metastases may invade the hepatic veins, thus establishing a further embolic cycle to the lungs. The media of arteries and medullated nerves both exhibit decided freedom from malignant invasion.

AUTHOR'S SUMMARY.

VARIATIONS IN THE GROWTH OF THE JENSEN RAT SARCOMA AND THE INFLUENCE OF TECHNIQUE. H. CHAMBERS and G. M. SCOTT, J. Path. & Bact. **33**:553, 1930.

Experiments are described which show that the transplanted Jensen rat sarcoma at the present time has in a pure breed stock many of the characteristics of a spontaneous malignant tumor. In 272 rats no tumor absorbed spontaneously; in a series of 52 rats, 86 per cent were successfully reinoculated and metastases were found in a large number. The rate of growth has considerably increased. Rats have been bred relatively immune to Jensen rat sarcoma. The capacity of tumor cells to produce immunity varies with the condition of the tumor from which the grafts are taken. To obtain comparable results with the Jensen rat sarcoma, the technic of transplantation needs careful and precise attention.

AUTHORS' SUMMARY.

AN EARLY TAR CANCER OF THE RABBIT'S EAR WITH PENETRATION OF THE CANCER CELLS INTO THE BLOOD VESSELS. A. BABES, Bull. Assoc. franç. p. l'étude du cancer **19**:162, 1930.

The internal surface of the ear of a female rabbit was painted with Roumanian tar, resulting in the appearance of a cancer within twenty days. The malignant disease was found on both sides of the painted ear. A biopsy revealed the presence of cancer in the circulation.

B. M. FRIED.

NEUROBLASTOMA OF THE FIRST BRANCH OF THE TRIGEMINUS. W. HACKEL, Frankfurt. Ztschr. f. Path. **40**:31, 1930.

In a woman, aged 43, a tumor was found in the middle cranial fossa, situated close to the left internal carotid artery and the sinus cavernosus, in the region of the third branch of the trigeminus. A few small meningiomas of the dura were also found. The main tumor consisted of ganglion cells, which in part were degenerated, neuroblasts, some of which were arranged in the form of rosettes, and a few neurogonia. Nerve fibers were demonstrated between the neuroblasts and the groups of ganglion cells. Several areas of necrosis were encountered in the peripheral portion of the tumor. There were accumulations of lymphoid cells about the blood vessels. The first branch of the trigeminus, partially infiltrated with tumor cells, was found in the sections of the marginal portions of the tumor. In accordance with the classification of von Fischer (*Frankfurt. Ztschr. f. Path.* **28**:663, 1922), this tumor is termed as an immature, infiltrating ganglioneuroma. A sympathetic heterotopia or remnants of a sympathetic anlage within the third branch of the trigeminus are regarded as the possible source of origin.

GROWTH OF THE ROUS SARCOMA. E. FRÄNKEL, Klin. Wchnschr. **9**:1064, 1930.

By the Willstätter method for the isolation of ferments and using aluminium hydroxide as absorbent, Fränkel recovered the active substance from filtrates of the Rous sarcoma.

AUTHOR'S SUMMARY.

PRIMARY MELANOBLASTOMA OF THE LIVER. M. BRANDT, Ztschr. f. Krebsforsch. **31**:254, 1930.

Two cases of melanoblastoma are here reported, one certainly primary in the liver and limited to that organ, the other probably primary there, but with dissemination to the spleen, the submucosa of the upper jejunum and the lungs. In the first case aggregations of typical stellate Kupffer cells were found in otherwise uninvolved portions of the liver, and some scattered pigmented cells were present in the splenic sinuses.

H. E. EGGERS.

Medicolegal Pathology

IDENTIFICATION OF ASSASSIN BY MICROSCOPE. BALTHAZARD, Ann. de méd. lég. **110**:73, 1930.

A man was shot with a revolver, the muzzle of which was held against the back of the head. The suspected murderer was identified by finding not only spots of human blood on the vest and trousers but also by finding on the vest bits of cerebellar tissue. The dried scales on the vest were soaked in salt solution for two hours and then embedded in paraffin and stained by Nissl's method.

CARBON MONOXIDE POISONING WITHOUT EXTINCTION OF FLAME UNDER WASH BOILER. F. NAVILLE and C. SOUTTER, Rev. méd. de la Suisse Rom. **50**:336, 1930.

The cause of four cases of fatal carbon monoxide poisoning under somewhat similar circumstances was investigated. In each case the victims were found in or near a room in which a washer had been left to boil over a gas burner. Blood tests showed 16.5, 16, 18 and 20 per cent, respectively, of carbon monoxide present. As there was no odor of fuel gas in the rooms, a search was made to discover the source of the gas. A simple experiment was made under the conditions that obtained in the four cases. This revealed that the carbon monoxide was formed immediately and not as a result of prolonged combustion. The steam from the boiler was in no way a contributing factor because, when the experiment was completed, the water in the boiler was scarcely warm. Fuel gas is composed

essentially of hydrogen, hydrocarbons and carbon monoxide; the first two burn at a lower temperature than carbon monoxide. The gas flame comes in contact with the bottom of the washer filled with water, spreads out and cools. The larger the metallic surface and the amount of water, the lower the temperature of the flame. The hydrogen and hydrocarbons, which are highly combustible, burn completely into water and carbon dioxide, but some of the carbon monoxide does not and passes off into the air. This, rather than a close atmosphere, or a deficiency in the oxygen consumed by the flame, was the cause of the four deaths. In the apparent utter harmlessness of all the apparatus involved as well as in the lack of any characteristic odor to warn of the presence of carbon monoxide lies the unsuspected menace, of which the public should be promptly warned.

THE PATHOLOGIC ANATOMY OF SEPTIC ABORTION. K. LÖWENTHAL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:265, 1930.

The routes of infection after abortion are discussed on the basis of a study of fifteen cases. Emphasis is placed on an ascending suppurative process in the pelvic connective tissue and psoas muscle following perforation of the anterior wall of the cervix. Fatal infection, primarily a peritonitis, may follow abortion but be due to the rupture of an existing suppurative focus. To detect minute perforations, microscopic examination may be necessary.

CONCERNING THE DETERMINATION OF THE TIME OF DEATH OF HUMAN BODIES. H. MERKEL, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:285, 1930.

This is a report at the meeting of Deutsches Gesellschaft für gerichtliche und soziale medizin, September, 1929, and the various phenomenon that tend to throw light on the question of the time of death are considered systematically. The details should be studied in the original. The special significance of the earliest possible observations on the dead body itself and its surroundings is emphasized.

THE EFFECT OF IRONING AND MANGLING ON THE DEMONSTRATION OF BLOOD SPOTS ON CLOTH. E. SCHECH, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:343, 1930.

Ironing and mangling reduce the solubility of blood coloring matter and proteins in blood stains. Potassium hydroxide requires a comparatively long time to extract the coloring matter from blood stains after ironing, and the demonstration of hemin crystals from blood spots that have been ironed may fail. The action of the heat in ironing does not completely hinder the precipitin reaction, but prolonged extraction with salt solution may be necessary on account of the reduced solubility of the serum proteins.

THE ASPIRATION AND DEGLUTITION OF BRAIN TISSUE AS EVIDENCE OF THE VITAL OCCURRENCE OF SEVERE INJURIES. K. WALCHER, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:398, 1930.

In severe injuries with extensive crushing of tissues it may be difficult if not impossible to decide whether the injury occurred during life or after death. Walcher describes four instances of extensive injuries to the head, three of which were due to motor trucks, in which pieces of brain tissue were aspirated deeply into the lungs and in two of the cases also swallowed. The aspiration and swallowing of brain tissue are regarded as showing clearly that the injuries in these cases were received during life.

DEATH BY STRANGULATION. LOCHTE, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:419, 1930.

This article is a detailed discussion of the importance of sinus caroticus (Hering) in cases of force on the neck (hanging, strangulation, boxing, etc.) in

which the autopsy observations appear to be negative. The person dies suddenly without passing through all the phases of asphyxiation (unconsciousness, dyspnea, convulsions, etc.) because of a reflex action, probably of the laryngeal nerve (laryngeal shock), on the heart. The compression of the sinus caroticus produces a ventricular fibrillation, and death may follow rapidly. Death occurring in persons in whom compression of the neck was negligible (of brief duration, slight force, etc.) is thus explained. In instances of strangulation, one may, therefore, meet two types of death: one due to a gradually ensuing asphyxiation accompanied by hemorrhages, or a shocklike death. The latter cases are of particular medicolegal importance as the results of the postmortem examination may be negative, or in other words, that it suggests sudden death from natural causes.

E. L. MILOSLAVICH.

MEDICOLEGAL SIGNIFICANCE OF DEATH FOLLOWING INJURIES IN SPORT. WALTER CREUTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:433, 1930.

Sudden death after a boxing match is often due to subdural hemorrhage, apparently because of the tearing of delicate pial veins. In one case, death occurred three months after the fight, and a recurrent internal hemorrhagic pachymeningitis was found. The skull may be fractured by a blow from a fist (Braine and Ravina). Trauma of the skull and brain were observed also in football players, who not uncommonly suffer fatal injuries to the spine. Traumatic laryngeal shock (sinus caroticus) with sudden death, and traumatic edema of the glottis are also considered. Blunt injuries to the abdomen (in football play, wrestling) may produce internal hemorrhage, peritonitis (transmigration of intestinal bacteria due to injury to the bowel) or tearing of the bowel. Injuries to the liver, spleen and kidney during athletics are also mentioned, the last as occurring particularly in football players. The legal question of contributory negligence, according to the German criminal law, is discussed.

E. L. MILOSLAVICH.

PERFORATION OF A SOLITARY ULCER OF THE INTESTINE. M. SAKORRAPHOS and B. PHOTAKIS, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:455, 1930.

This article is a description of a perforating ulcer of the ascending colon in a man, aged 64, and of a similar single ulcer in the jejunum of a man, aged 58. This ulcerous process in each case seems to have resulted from a necrotic infarct of the intestinal wall, since the ulcer was irregularly shaped and showed ragged edges.

E. L. MILOSLAVICH.

NITROBENZENE POISONING AND HEMORRHAGIC ENCEPHALITIS. EDUARD GÜNTZ, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:461, 1930.

A woman, aged 25, took nitrobenzene to induce menstruation. Soon after, an anesthesia-like unconsciousness followed, as a result of the action of the benzene, from which the patient recovered the next day. Alarming symptoms — cyanosis, dyspnea and disintegration of the blood (icterus) — gradually set in. Necropsy disclosed clotted blood in the veins and arteries because of a general capillary thrombosis, and a diffuse hemorrhagic encephalitis ascribed to toxic damage to the vessels.

E. L. MILOSLAVICH.

DETERMINATION OF BLOOD GROUPS IN BLOOD SPOTS IN CRIMINAL CASES. K. FUJIWARA, Deutsche Ztschr. f. d. ges. gerichtl. Med. **15**:470, 1930.

Three cases are described in which the determination of the blood groups of spots of blood on the clothing of persons suspected of crime gave valuable and significant results. In the fourth case, the determination of the group of seminal spots proved of value.

Society Transactions

PATHOLOGICAL SOCIETY OF PHILADELPHIA

Annual Gross Lecture, Nov. 13, 1930

BALDWIN LUCKÉ, M.D., *President, in the Chair*

EXPERIMENTAL CANCER (SUMMARY). WILLIAM H. WOGLOM.

A number of factors once thought to be responsible for malignant disease, such as diet, soil and climate, have been gradually eliminated, and of them all only chronic irritation now seems significant.

The connection between malignant disease and chronic irritation had been suspected for years purely on observational grounds, and recent experimental work has greatly strengthened the presumption. Yet chronic irritation alone cannot be the sole cause, for some of the most irritating substances are devoid of carcinogenic activity, while less irritating ones, like tar, produce cancer readily in certain families of animals but not in others. It is evident that between the tissue and the irritant there is some adaptation of a delicacy hitherto unsuspected, and of which nothing is known, that is essential to the production of malignant growth.

Neither morphology nor chemistry has yet disclosed any characteristic difference between the cancer cell and other vigorously proliferating elements.

Though the subject of immunity to transplantable neoplasms has been eagerly investigated for thirty years, it has yielded no information that could possibly be of the slightest practical value at the present time. It is hardly necessary to state that no specific test or method of treatment has been devised so far, and that except for the alleviating and occasionally curative effect of radiotherapy, surgical intervention remains our only hope.

Nevertheless, there is no reason to despair, for more accurate knowledge has been gathered during the past thirty years of experimentation than was accumulated throughout the preceding thirty centuries of observation.

Dec. 11, 1930

BALDWIN LUCKÉ, M.D., *President, in the Chair*

SCIENTIFIC MICROSCOPY. MAX POSER.

In scientific microscopy certain optical laws must be fulfilled in order to avoid false images caused by diffraction effects producing more or less optical illusions as compared with the real structure of a microscopic object. These optical laws are well defined in the report of the research work carried on by the late Professor Abbe, and it was the aim of Dr. Poser to discuss briefly the vital points pertaining to this investigation.

1. A homogeneous source of light is an essential factor in reliable microscopy, and the method of illumination must be adapted to suit the microscopic object under investigation.

2. In order to determine the resolution of an optical system of a microscope, the magnification is only a secondary factor, but the numerical aperture of the microscope objective is directly responsible for the resolution of the minute

details of the object. This is explained by the fact that a microscopic image consists of two kinds of images: (1) the image formed by the dioptric beam, which refers chiefly to the contour of the object, (2) and that of the more minute details in the structure of a microscopic object, which are rendered visible by means of the diffracted light beam caused by the object itself.

3. The term "aperture" of a microscope system is applicable only when dry objectives are involved. Regarding the determination of the resolution of the microscope with oil-immersion systems, the numerical aperture will furnish the correct information as to the resolution. It is therefore advisable to employ universally for low or high power work with the microscope the term "numerical aperture" when determining the resolving power of the optical system of the microscope, since this term applies to both low and high power microscope objectives.

4. The wave length of light is another factor of importance, since light of the shorter wave length of light in the spectrum used for illumination has a direct bearing on the resolving power of the objective.

5. The full illuminating cone should always be employed with stained objects, such as bacteria and other minute organic substances, while a greater penetrating power of the microscope system is essential with tissues of considerable depth of the section. From this it follows that the numerical aperture of the illuminating cone must be somewhat restricted, and thus the resolving power of a given optical system will be more or less limited.

6. Maximum contrast of the object under the microscope and the surrounding area cannot always be obtained with the staining of the object. A study of desirable light filters is therefore indicated in order to illuminate with light representing different color bands of the spectrum so chosen that the color of light selected for illumination in a given case neutralizes or absorbs the color of the staining solution and thus makes the object appear dark on a light background with direct illumination.

7. To examine living objects with dark ground illumination will be found useful in many cases in which living objects are to be investigated, and the best results are always obtained when light cones of extreme numerical aperture with the central beam cut out by an opaque stop of the desired dimension are used for the illumination of the object; with this kind of examination, the rule should be that the central stop and illuminating cone are so chosen that no direct light enters the objective.

8. When examining objects under the microscope with ultraviolet light, interesting results are obtained in all cases in which the medium in which the object is mounted or embedded does not absorb the ultraviolet light.

9. A given resolving power of an objective can almost be doubled when ultraviolet light of the shorter wave lengths is used for illumination, but such microscope lenses must then be made of quartz instead of glass, owing to the latter being more or less opaque to ultraviolet light of the shorter wave length.

10. When illuminated with ultraviolet light, objects showing fluorescence, luminescence or phosphorescence present an interesting study when examined in this manner, particularly in cases in which living specimens come into consideration.

Book Reviews

LABORATORY MEDICINE. A GUIDE FOR STUDENTS AND PRACTITIONERS. By DANIEL NICHOLSON, M.D., Member of the Royal College of Physicians, London; Assistant Professor of Pathology, University of Manitoba; Assistant in Pathology, Winnipeg General Hospital. Cloth. Price, $6, net. Pp. 437, with 108 engravings and a colored plate. Philadelphia: Lea & Febiger, 1930.

The object of this book is to describe and interpret diagnostic laboratory tests and procedures. The first few pages outline briefly the tests that are indicated under various general conditions and are followed by chapters on the various tests of the blood, exudates and puncture fluids, sputum, cerebrospinal fluid, gastric and duodenal contents, urine and feces, on cutaneous tests, reactions of immunity and miscellaneous examinations (basal metabolism, biopsy, poisons), and finally on laboratory equipment. The book contains a great deal of useful information for the physician as well as for the clinical pathologist. On the inside front cover are given important normal standards. The author does not consider the details of the microscopic examination of tissues for diagnostic purposes. The statement on page 114, that Hodgkin's disease "is probably caused by the avian tubercle bacillus," seems at least premature. On page 195, ricineolated antigen is listed as of proved value in protecting against scarlet fever, but its value is far from proved. Under examination of the skin for fungous disease (p. 335) there is no mention of blastomycosis or sporotrichosis. Chapter 12, on reactions of immunity, is valuable; in the next edition it should be revised with great care and enlarged to include the agglutination and Wassermann tests, which are now described in another chapter. Kahn's test and also agglutination tests for tularemia and brucellosis are not even mentioned. The description of vaccination against smallpox and the subsequent reactions is excellent. The statements about the diagnosis of infantile paralysis in the preparalytic stage, in which examination of the spinal fluid is so important, should be elaborated, and the method of injecting convalescent serum brought to date. By perfecting himself in the tests and procedures of known value in the diagnosis, prevention and treatment of infectious diseases, the physician and clinical pathologist can greatly increase their usefulness.

A COMPILATION OF CULTURE MEDIA FOR THE CULTIVATION OF MICROORGANISMS. By MAX LEVINE and H. W. SCHOENLEIN. Cloth. Price, $15. Pp. 969, with 7,000 formulas and four indexes. Baltimore: Williams & Wilkins Company, 1930.

This compilation of culture mediums has been "prepared at the request of the Society of American Bacteriologists and financed by a grant from the Digestive Ferments Company, Detroit, Mich." Seven thousand formulas have been grouped into approximately 2,500 mediums, the constituents, preparation and use of which are described. The mediums are numbered consecutively but subdivided into 7 groups according to their physical states. For each group there is a key by means of which the individual mediums may be located. There are several indexes: medium name index, constituents index, which lists every medium in which a particular substance is used, an author index, a use index, listing the mediums "for which a specific use was indicated in the original article reviewed" and, finally, the list of references. In the constituents index are long lists of numbers of mediums containing substances in frequent use, e. g., calcium chloride, dextrose, glycerol, magnesium sulphate, potassium phosphate and sodium chloride. It is not clear what value such lists can have, but there is no question about the value of

the book as a whole. An enormous amount of useful information in bacteriologic work has been collected and indexed. The entire experience in the making of mediums since Koch's day is summarized. The originators and authors of the book deserve high credit.

J. GEORGE ADAMI. Sometime Strathcona Professor of Pathology McGill University, Montreal. A Memoir. By Marie Adami together with contributions from others, his friends, and an Introduction by Sir Humphry Rolleston Bart, G.C.V.O., K.C.B., M.D. Price, $3.50. Pp. 179. New York: Richard R. Smith, Inc., 1930.

American pathologists and physicians know J. George Adami best from his work and influence while professor of pathology (1892-1914) in McGill University. Many of them were deeply impressed by his philosophical articles on inflammation (1896) and on inheritance and disease (1907), as well as by his emphasis on pathology as a branch of biologic science and his activities in enforcing its bearings on medical practice and public health. He was, in fact, one of the most influential leaders in medicine on this side of the Atlantic when the World War called him back to England. The memoir, written by his widow but supplemented by contributions from fellow-workers and by a bibliography of his printed works, deals successively with his life and early work in Cambridge, with his Canadian period, his services during the war and his efficient activities as vice-chancellor of the University of Liverpool. A many-sided and charming personality stands forth clearly. The diminishing band of Adami's contemporaries and his pupils will read the memoir with grateful interest. As a worthy and appropriate record of "an exceptionally gifted leader in pathological and general education" it will have a wide appeal.

Books Received

MOLDS, YEASTS, AND ACTINOMYCETES: A HANDBOOK FOR STUDENTS OF BACTERIOLOGY. By Arthur T. Henrici, M.D., Professor of Bacteriology, University of Minnesota. Price, Cloth, $3.50 net. Pp. 296, with 100 illustrations. New York: John Wiley & Sons, Inc., 1930.

MEDICAL BIOMETRY AND STATISTICS. By Raymond Pearl, Ph.D., Sc.D., LL.D., Professor of Biology in the School of Hygiene and Public Health, and in the Medical School, Johns Hopkins University, Baltimore. Edition 2. Price, cloth, $5.50. Pp. 459. Philadelphia: W. B. Saunders Company, 1930.

UEBER DAS PROBLEM DER BÖSARTIGEN GESCHWÜLSTE. EINE EXPERIMENTELLE UND THEORETISCHE UNTERSUCHUNG. Von Professor Dr. Lothar Heidenhain, in Worms. Volume 2. Royal quarto. Price, unbound, 42 marks; bound, 47.50 marks. Pp. 207, with 229 illustrations. Berlin: Julius Springer, 1930.

THE MOVEMENTS OF THE EYES IN READING. Medical Research Council Special Report Series, no. 148. By M. D. Vernon. Price, 9 pence net. Pp. 45. London: His Majesty's Stationery Office, 1930.

TECHNIQUES HISTOLOGIQUES DE NEUROPATHOLOGIE. Par Ivan Bertrand, Derecteur à l'École pratique des Hautes Études, Chef de Laboratoire de la Clinique Neurologique de la Salpétrière. Préface du Professeur G. Guillain. Price, 50 francs. Pp. 376. Paris: Masson et Cie, 1930.

NOSOGRAPHY: THE EVOLUTION OF CLINICAL MEDICINE IN MODERN TIMES. By Knud Faber, M.D., LL.D., Professor of Internal Medicine, University of Copenhagen. With an Introductory Note by Rufus Cole, M.D., Director of Hospital, Rockefeller Institute. Edition 2. Price, $3.75. Pp. 222, with 22 illustrations. New York: Paul B. Hoeber, Inc., 1930.

METHODS AND PROBLEMS OF MEDICAL EDUCATION (EIGHTEENTH SERIES). New York: The Rockefeller Foundation, 1930.

ANNUAL MEDICAL REPORT OF THE CHICAGO TUBERCULOSIS INSTITUTE AND THE EDWARD SANATORIUM, 1929-1930.

GEWEBSPROLIFERATION UND SÄUREBASENGLEICHGEWICHT. Von Dr. Rudolf Balint, O. Ö. Universitäts-Professor, Direktor der I. Medizinische Klinik der Pázmány Pèter-Universität in Budapest und Dr. Stefan Weiss Assistent der I. Medizinische Klinik der Pázmány Péter-Universität in Budapest. Mit einem vorwort von Baron A. von Korànyi O. Ö. Universitäts-Professor Direktor der III. Medizinische Klinik der Pázmány Péter-Universität in Budapest. Price, unbound, 16.80 marks; bound, 18.40 marks. Pp. 209, with 59 illustrations. Berlin and Vienna: Julius Springer, 1930.

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